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Aspects of Neoadjuvant Therapy in the Curative Treatment of Cancer in the Esophagus or Gastroesophageal Junction

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“Outside of a dog, a book is a man’s best friend.
Inside of a dog it’s too dark to read”
- Groucho Marx

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ABSTRACT

Malignant esophageal tumors are among the most severe cancers. Only about 30% of the patients are suitable for curative treatment at diagnosis. The treatment is extremely demanding and unfortunately has disappointing results. The staging of disease and the treatment for cancer of the esophagus and gastroesophageal junction need to be improved. It is currently well established that neoadjuvant therapy, either with chemotherapy or with combined chemo- and radiotherapy, followed by surgery, offers a better chance for a cure in stage II and III esophageal and gastroesophageal junction cancer, than surgery alone. Data directly comparing neoadjuvant chemotherapy and chemoradiotherapy are scarce and it is debatable which of these neoadjuvant treatment concepts offers the best chance for long-term survival.

This thesis aims to improve the knowledge about neoadjuvant treatment in the curative treatment of esophageal cancer. Papers I and III were based on the Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Esophagus and Gastric Cardia (NeoRes) trial, which was performed in Norway and Sweden during the period 2006–2013. Patients with resectable squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction were randomized to either preoperative chemotherapy or preoperative combined chemoradiotherapy followed by surgical resection. Paper I showed an increased risk for severe postoperative complications after chemoradiotherapy compared to chemotherapy. In paper III we found that neoadjuvant chemoradiotherapy significantly increases the proportion of complete histological response, increases the occurrence of N0 lymph-node status, and increases the R0 resection rate, but there was no difference in overall survival compared to neoadjuvant chemotherapy.

Paper II is a retrospective cohort study of patients with cancer of the esophagus or gastro-esophageal junction, who was reconstructed with cervical anastomosis. The planned radiation dose to the site of the cervical anastomosis on the gastric fundus was estimated for each patient. This study suggests that nCRT exposes the future anastomotic site to doses of radiation that may impair healing of the subsequent cervical anastomosis. Our data further suggest that nCRT may increase the severity of cervical anastomotic complications.

Paper IV is a prospective population-based cohort study including all patients who underwent an esophagectomy operation due to cancer in Sweden, excluding T1N0, recorded in the Swedish National Register for Esophageal and Gastric Cancer, 2006-2014. The results showed that neoadjuvant chemoradiotherapy increases local tumor control, represented by increased R0 resection rates and pathological node-negative disease both compared to surgery alone and chemotherapy. For patients with the histological subtype squamous cell carcinoma, neoadjuvant treatment increases long-term survival but also increases the risk of postoperative morbidity and mortality compared to surgery alone. Neither of the two neoadjuvant treatment options seem to improve survival in adenocarcinomas, compared to surgery alone, in an unselected population of patients.

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LIST OF SCIENTIFIC PAPERS

I. **Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation.**
Klevebro F, Johnsen G, Johnson E, Viste A, Myrnas T, Szabo E, Jacobsen, A. B, Friesland, S, Tsai, J. A, Persson, S, Lindblad, M, Lundell, L, Nilsson, M. European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015 Jul;41(7):920-6. PubMed PMID: 25908010.

II. **Neoadjuvant chemoradiotherapy may increase the risk of severe anastomotic complications after esophagectomy with cervical anastomosis.**
Klevebro F, Friesland S, Hedman M, Tsai JA, Lindblad M, Rouvelas I, et al. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2016 Mar 28. PubMed PMID: 27020672. Epub 2016/03/30.

III. **A Randomised Clinical Trial of Neoadjuvant Chemotherapy vs. Neoadjuvant Chemoradiotherapy for Cancer of the Oesophagus or Gastro-Oesophageal Junction.**
Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen A-B, Friesland S, Hatlevoll I, Glenjen NI, Lind P, Tsai JA, Lundell L, Nilsson M Annals of Oncology. 2016 Jan 17. PubMed PMID: 26782957.

IV. **Neoadjuvant therapy for cancer of the oesophagus or gastro-oesophageal junction - Swedish population-based national register data.**
Fredrik Klevebro, Mats Lindblad, Jan Johansson, Lars Lundell, Magnus Nilsson.
Submitted.

CONTENTS

LIST OF ABBREVIATIONS

nCT	Neoadjuvant chemotherapy
nCRT	Neoadjuvant chemoradiotherapy
SA	Surgery alone
dCRT	Definitive chemoradiotherapy
SCC	Squamous cell carcinoma
AC	Adenocarcinoma
GEJ	Gastroesophageal junction
ASA	American Society of Anesthesiologists
RCT	Randomized controlled trial
CD	Clavien-Dindo
FDG-PET	Fluorodeoxyglucose positron emission tomography
5-FU	5-fluorouracil
CT	Computed tomography
N stage	Lymph node stage
T stage	Tumor stage
ARDS	Acute respiratory distress syndrome
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
NeoRes	Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Esophagus and Gastric Cardia trial
LET	Linear energy transfer
Gy	Gray (joule/kg)
TCP	Tumor control probability
NTCP	Normal tissue complication probability
GTV	Gross tumor target volume
CTV	Clinical target volume
PTV	Planning target volume
JCOG	Japan Clinical Oncology Group
ECOG	Eastern Cooperative Oncology Group
UICC	Union for International Cancer Control
CCI	Comprehensive Complication Index

1 INTRODUCTION

1.1 EPIDEMIOLOGY OF ESOPHAGEAL CANCER

Esophageal cancer is a rare disease but it is the sixth most common cause of cancer death in the world, over the past decades the incidence has changed. There are about 500,000 patients diagnosed each year worldwide (1, 2). The most common histological types are squamous cell carcinoma (SCC) and adenocarcinoma (AC) representing more than 90% of the tumors. Less frequent types are melanoma, leiomyosarcoma, malignant neuroendocrine tumors and lymphomas.

The incidence of AC is rising faster than any other malignancy in the Western world and at the same time the incidence for SCC is slowly decreasing (3-5). The causes of these changes are not completely known. SCC is more common in developing countries and is associated with smoking, alcohol consumption and low socioeconomic status. SCC is still the most common histology but in the western world AC now comprises the majority of cases (6). Increasing prevalence of obesity and gastroesophageal reflux explains some of the increase. Oxidative stress and chronic inflammation in the mucous membrane of the esophagus seems to be related to the development of both AC and SCC but through different pathways (7, 8). In Sweden men currently have an incidence of 3.9/100,000 for AC and 1.8/100,000 for SCC. The incidence for women in Sweden is 1.8/100,000 for AC and 1.0/100,000 for SCC. The reasons for the difference between the genders are mainly unknown (9).

Barrett's columnar lined esophagus is a condition which is characterized by intestinal metaplasia in the distal esophagus recognized by endoscopy and verified with biopsy (10). In Barrett's esophagus the normal squamous cell epithelium has been replaced by metaplastic columnar epithelium, the type of epithelium normally found in the ileum and colon. This is thought to be caused by long-term exposure to content from the stomach due to reflux. The condition is associated with an increased risk of developing AC from 0.1-6% per year (11, 12). Patients with Barrett´s esophagus undergo regular endoscopies in order to avoid the development of cancer. Surveillance programs to detect the condition among risk patients have been suggested but are not commonly used (13).

1.2 CLINICAL PRESENTATION AND WORK-UP

The most important symptom of esophageal cancer is a problem with swallowing, so-called dysphagia, which occurs when the tumor engages about 2/3 of the circumference of the lumen. Initially solid foods are difficult to swallow; eventually this progresses to include fluids. Patients often lose weight, sometimes leading to sarcopenia. Other symptoms can include dyspnea, epigastric or retrosternal pain, persistent cough, respiratory symptoms, or hoarseness. The investigation starts with an endoscopic examination of the esophagus, and stomach (esophagogastroduodenoscopy). Biopsies are taken for cytological evaluation, which concludes the diagnosis. Before treatment the patient is examined with computed tomography (CT) of the chest and abdomen to evaluate the tumor and screen for metastases and enlarged

lymph nodes (N-stage). Endoscopic ultrasound has a slightly higher accuracy for determining N-stage compared to CT (14). The clinical tumor stage (T-stage) is assessed with the use of computed tomography and endoscopic ultrasound. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is a nuclear functional imaging technique that can measure the local metabolic activity in the body. It can be used to find metastases from cancer and also to evaluate response to an oncological treatment. FDG-PET can be combined with a computed tomography to create three-dimensional images. In esophageal cancer FDG-PET-CT is sometimes used for staging the disease preoperatively (15). In patients with advanced tumor, stages T3-T4, in the GEJ a laparoscopy can improve the accuracy of the clinical staging. The clinically evaluated T-stage is incorrect in about 40% of the patients (16). A higher T-stage is associated with decreased survival (17, 18).

Before the decision about therapy can be made the patients need a thorough physical examination and control of comorbidities. An exercise stress test on a bicycle gives a measure of the physical performance level. Spirometry is used to evaluate the pulmonary function. In many cases the patients are unfortunately not fit enough for surgery, alternatively the tumor growth is locally advanced or has distant metastases. Palliative oncological treatment and best supportive care will then be applied.

1.3 SURGICAL TREATMENT

Surgical resection, when possible, has been the accepted first treatment choice for decades. The esophagectomy is technically advanced and has one of the highest risks of complications and postoperative mortality of all surgical procedures but it offers the best chance for long-term survival (4, 19).

Superficial tumors that do not penetrate through the submucosa can be removed with endoscopic resection with similar chances of long-term survival as esophagectomy (20). Endoscopic mucosal resection (EMR), first developed in Japan for early gastric cancers, is now used worldwide for removal of adenomas and local tumors in the rectum, colon and the esophagus. The lesion is identified and demarked, and then a submucosal injection is used to lift the mucosa from the submucosa before resection with a snare through an endoscope. An alternative technique is the endoscopic submucosal dissection (ESD) which has been reported to increase the chance for en-bloc complete resection of the neoplastic lesions (21). ESD applies endoscopic dissection with a diathermic knife instead of the snare used in EMR, making resection of larger lesions possible. T1a tumors have a very low risk of spreading to local lymph nodes and it is feasible to treat them with endoscopic resection. T1b tumors have increased risk of lymph node metastases, therefore esophagectomy with lymph node dissection is recommended in these cases. Endoscopic resection has the advantage of sparing the patient from an esophagectomy. The R0 resection rate is around 90%, or higher for tumors smaller than 25 mm diameter, and the risk for perforation is around 1% (22). Definitive chemoradiotherapy for stage I esophageal SCC has been investigated in Japan with a 4-year survival rate of 80.5% (23).

The history of the esophagectomy started in the late 19th century with Theodor Billroth, who performed the first resection of the esophagus via the abdomen in 1871. The first successful resection of the thoracic part of the distal esophagus was performed in 1913 by Franz J. A. Torek in New York. The patient was a 67-year-old female with a distal squamous cell carcinoma. The tumor was exposed through a left-side thoracotomy in the seventh intercostal space. The tumor was removed and the proximal part of the esophagus was brought out subcutaneously below the neck. The proximal esophagus was connected with a gastrostomy rubber tube and the patient could eat orally. This was a new approach in entering the thoracic cavity and a major surgical breakthrough. The patient was cured from the cancer and lived for 12 more years (24, 25).

The overall 5-year survival rate for esophageal cancer has increased from less than 5% in the 1970s and is currently 15-25% (26, 27). The reasons for the poor prognosis are that the disease is often disseminated by the time of detection, because early stage disease rarely causes symptoms, and that the curative treatment is extremely demanding and often not tolerable for elderly and chronically ill patients (19). Less than 50% of all patients are suitable for treatment with curative intent. Surgical resection of the tumors with limited spread offers a 5-year survival rate of about 25-30% (28-30). Enhanced recovery programs with improvements in perioperative care have been introduced and more patients are now being treated in high-volume centers specializing in esophageal cancer, all together leading to improved outcomes (31, 32).

1.3.1 Surgical technique

Esophagectomy may be performed using a variety of techniques. In order to cure a patient from cancer the tumor needs to be removed with a margin of healthy tissue surrounding the specimen, in other words an R0 resection. The College of American Pathologists define an R0 resection as no tumor cells present at the border of the specimen. The Royal College of Pathologists define R0 resection as no tumor cells within 1 mm of the margin (33-35). The differences in classification are important when comparing the results of studies. Tumor-free circumferential margin is most difficult to achieve whereas the longitudinal margins are tumor free in the majority of cases. A so-called R1 resection with microscopically identified tumor cells at the resection margin is associated with poor outcome (17, 36). In the situation where it is impossible for the surgeon to remove all macroscopically visible tumor the resection is defined as R2.

In Western populations, with the dominance of distal adenocarcinomas, the most used technique is the two-stage thoraco-abdominal Ivor Lewis procedure first described in 1946. The stomach and distal esophagus are dissected via a laparotomy and the mediastinal part of the esophagus through a right-sided thoracotomy. The anastomosis is placed just below the thoracic aperture. The advantages of the Ivor Lewis approach are the good access to the tumor and lymph nodes in the thorax and decreased risk of recurrent nerve injury compared to procedures involving a cervical incision. On the other hand placing the anastomosis in the thorax carries the risk of life-threatening mediastinitis in the case of anastomotic failure. The

thoracotomy is associated with postoperative pulmonary complications and the proximal surgical resection margin is on average shorter than with a cervical incision (37). Transhiatal esophagectomy, initially described by Denk in 1913, employs access only through a laparotomy and a neck incision and using a cervical anastomosis of the gastric conduit for reconstruction. This approach has the benefit of avoiding thoracotomy, leading to less pulmonary complications and is often used in patients who are not fit enough for the Ivor Lewis esophagectomy. The downside is of course that the dissection of the thoracic part of the esophagus is performed from the abdomen with less precise lymph node dissection, especially in the mid and upper mediastinum, resulting in fewer resected lymph nodes and, with the possible exception of Siewert II junctional cancers, a lower chance for long-term survival (38, 39). The cervical approach increases the risk of recurrent nerve injury (40). The proximal esophagus is reached through an incision in the neck and the anastomosis is constructed here. An advantage with this technique is that in the case of an anastomotic leakage it can be drained through the wound on the neck and mediastinitis can in many cases be avoided.

In Asia, with the high incidence of squamous cell carcinoma of the upper and mid esophagus, the three-stage esophagectomy with incisions in the right thoracic cavity, abdomen and neck with cervical anastomosis is the most common technique. This procedure was first described by McKeown in 1976. The advantages with the approach are good access for removing the whole esophagus, improved possibilities to perform a radical lymphadenectomy, including the option of radical neck dissection, and the placement of the anastomosis out of the thorax (41). Disadvantages are increased postoperative morbidity due to the large operating field (42). In Asia the three-field lymphadenectomy is widely used, in the western world it is mainly applied in cases with known lymph node metastases (43, 44).

Recently minimally invasive procedures have been developed, using laparoscopic and/or thoracoscopic access (45). The techniques correspond to the two-stage Ivor Lewis esophagectomy, transhiatal esophagectomy, or the three-field dissection esophagectomy. The anastomosis can be constructed in the thorax, using circular or linear stapling technique, or hand-sewn in the neck through a cervical incision. Trials show evidence of better short-term outcomes after minimally invasive techniques compared to open esophagectomy. In particular pulmonary and respiratory complications have been shown to be reduced (46-48). Hybrid minimally invasive esophagectomy with laparoscopy and thoracotomy have been shown to have good results concerning major pulmonary complications and a decreased rate of postoperative mortality compared to surgery alone (SA) (49, 50). Robot-assisted esophagectomy has been introduced in some centers and is under development (51, 52).
The most common technique for reconstruction is the gastric tube conduit. With the use of linear staplers a tube is formed of the greater curvature side of the stomach. The conduit is then pulled up to the proximal esophagus and an anastomosis is performed in the thorax or in the neck. Long term results have been shown to be similar comparing intrathoracic and cervical anastomoses in a non-randomized study (53). A potential problem with the use of a gastric conduit is that the circulation may be compromised in the proximal part where the

anastomosis will be situated. The gastroepiploic artery and vein, and the first two or three branches of the right gastric arteries and veins are preserved and the dissection of the major curve is made with caution in order to decrease the risk for poor circulation and subsequent necrosis in the anastomosis.

Figure 1. *A gastric tube during construction.*

When applying a cervical anastomosis the gastric conduit often has to be used in its full length, constructing the anastomosis at the most cranial part of the fundus of the stomach, where the circulation is most limited. If the conduit can be made longer than needed the most cranial few centimetres can be resected. Deficient circulation may account for the increased risk of leakage and postoperative stricture, which has been observed in some studies comparing cervical and intrathoracic anastomoses (54-56). Moreover, patients with distal tumors being irradiated preoperatively within the context of nCRT, run a risk of receiving biologically relevant doses of radiation directly against the gastric fundus, which is subsequently used for the anastomosis. Radiotherapy towards distal esophageal tumors is administered with relatively generous margins in order to compensate for breathing-related movement in the area. The coeliac lymph nodes are also included in the field. Dose planning to reduce the dose against heart and lung is performed, but the fundus part of the stomach that will be used in the esophagogastrostomy is not actively avoided. This may further increase the risk and severity of cervical anastomotic complications, given the already compromised circulation of the extended gastric conduit necessary to reach the neck.

1.3.2 Postoperative complications

The perioperative mortality rate after esophagectomy is among the highest of all surgical procedures but it has improved over the years, from 29% 1960-1979 to 8.8% 1990-2000 (30, 57, 58). Hospitals that perform many esophagectomies (high volume centers often defined as >10 esophagectomies/year) have better results in terms of both postoperative morbidity and mortality as well as long-term survival (32, 59). In high volume centers the perioperative mortality is now around 3% (60-62). One study identified an increased use of epidural analgesia, bronchoscopy to clear the lungs from secretion, decreased frequency of smoking, and less perioperative bleeding as factors associated with less in-hospital mortality after esophagectomy (63). The overall rate of postoperative complications is between 40-80% in different studies partly depending on definition and method of assessment. American Society of Anesthesiologists (ASA) score, male gender, cervical anastomosis, and high age are known risk factors for postoperative morbidity and mortality (64, 65). It is difficult to compare trials concerning complications due to the different classifications. A standardized report system could improve the studies of postoperative outcomes (66). The Esophageal Complications Consensus Group has proposed a recommended list of variables and definitions of postoperative events that should be recorded in studies after esophagectomy in the future (67). Enhanced recovery programs are now being introduced in many centers. The scientific evidence for using these programs is relatively weak but the guidelines in the programs are all based on the best available evidence. The programs have probably improved the postoperative care and reduced the treatment-related morbidity and mortality (31). Anastomotic failure is one of the most severe complications and occurs in about 10% (68) of the cases with the Ivor Lewis technique and 15-35% with neck anastomosis, many times with complicated postoperative care with single or multi-organ dysfunction or even death as a result (55, 56, 64, 69, 70). A leakage from the anastomosis can cause severe mediastinitis leading to a large inflammatory response, acute respiratory distress syndrome (ARDS), and respiratory insufficiency. It is important to discover an anastomotic leakage early and often to treat it aggressively. Endoscopic evaluation of the anastomosis should be done if there is suspicion of a leakage. Treatment options are conservative; with the use of stent and intrathoracic drainage or lavage, or in the worst case rescue esophagectomy (69, 71, 72). In this procedure the anastomosis is removed and the esophagus is deviated in a stoma on the neck.

Pulmonary complications after esophagectomy are a major concern. It occurs in about 20% of the patients after open surgery. Pneumonia, intrathoracic abscess, thoracic duct injury, and pneumo- or hemothorax are reasons for impaired pulmonary function and sometimes respiratory insufficiency requiring ICU-care. Anastomotic failure increases the risk of pulmonary problems. A randomized clinical trial (RCT), of minimally invasive techniques with thoracoscopy, has shown a decreased rate of pulmonary complications to 9% compared to 29% in the open surgery group (46).

Severe cardiovascular complications after esophagectomy are not common but may cause serious problems in 5-10% of the patients. The most common cardiovascular complication is

postoperative atrial fibrillation which occurs in 20-25% of the patients (73). Atrial fibrillation is sometimes a symptom of another serious complication or a result of either over-hydration or hypovolemia.

Thromboembolic complications are not a major problem in terms of severity of outcome, but sufficient prophylaxis with low-molecular weight heparin is indicated, as thromboembolic events with minor, or even no symptoms, are very common (58). Bleeding can be a major problem intraoperatively by unintended damage to, for example, the azygos vein, inferior pulmonary vein, splenic artery or even the aorta. This is however very rare. Delayed postoperative bleeding can occur 24-48 hours after surgery and can be caused by slipping of ties or clips from gastric vessels or bronchoesophageal arteries or veins.

Postoperative benign anastomotic strictures occur in about 20% of the patients after hand-sewn or circular stapled intrathoracic anastomosis. The frequency is around 30% in cervical anastomoses (74). The strictures can usually be managed by one or several endoscopic balloon dilatations (75). Postoperative complications and preoperatively decreased arterial oxygen levels have been identified as risk factors for postoperative stricture (76). Recurrent nerve paralysis occurs in about 15% of the cases and is associated with an increased risk of pulmonary complications (40).

1.4 ALTERNATIVE TREATMENT STRATEGIES

As prognosis has remained poor despite considerable improvements in perioperative care and short-term outcomes, efforts have been made to introduce additional therapy (77). The use of adjuvant therapy options have been disappointing; this may be at least partly attributed to difficulty in tolerating demanding therapy shortly after esophagectomy (28, 78-82). Cervical tumors are uncommon and represent about 5% of all esophageal tumors. The surgical approach to the cervical tumor may require laryngopharyngoesophagectomy which disrupts the patient´s speech and sometime swallowing. Curatively intended radiotherapy or chemoradiotherapy can be used in these patients (83). Radiotherapy is useful in the palliative situation for locoregional disease control and symptom relief. During the 1980s some trials investigated the effect of neoadjuvant radiotherapy but the results were not comparable to those of nCT (84, 85).

Histological tumor type SCC has been shown to have better response to chemoradiotherapy than AC (86, 87). Definitive chemoradiotherapy (dCRT) for SCC gives overall survival rate that is on a similar level as after SA and is an alternative treatment regimen for these patients (88, 89). A trial evaluating the effect of surgery, compared to continued CRT, in patients who responded to nCRT with tumor regression showed no survival benefit from esophagectomy (90). A problem with dCRT is that there are no certain ways to determine that a patient has a complete response without performing an esophagectomy. A meta-analysis of the diagnostic accuracy of endoscopic biopsy and EUS has shown that the technique has high specificity but low sensitivity to detect residual disease after neoadjuvant treatment (91). A recent study has evaluated the outcomes in 848 patients treated with salvage esophagectomy, due to persistent

or recurrent disease within 3 months of dCRT, compared to nCRT and planned esophagectomy. There was an increased risk of anastomotic leak and surgical site infection in the salvage esophagectomy group. There was, however, no difference in overall survival or postoperative mortality (92).

1.4.1 Adjuvant treatment

Adjuvant treatments with chemotherapy or chemoradiotherapy are used in some cases but have not been shown to increase survival (78-80, 93, 94). A major problem is that patients have traditionally had a long recovery period after esophagectomy, making adjuvant oncological treatment not suitable for the majority of patients. In a small trial by Chen and colleagues postoperative radiotherapy was given to patients with pathologically confirmed lymph node metastases. The results showed decreased risk of recurrence within the irradiated field compared to lymph node negative patients who did not receive radiotherapy. There was no increase in survival (95). Most esophageal cancer recurrences are not limited to local lymph nodes or anastomotic failure, which makes the rationale for adjuvant radiotherapy weak (96). Zahoor and colleagues performed a retrospective study of 375 patients comparing primary minimally invasive esophagectomy and adjuvant chemotherapy to nCT and surgical resection with similar survival in both groups (97). Most centers do not operate on patients with M1 disease, however, a recent study has shown that neoadjuvant treatment followed by resection is feasible in some patients (98). Survival after recurrence is very poor but in some selected cases a surgical resection and oncological treatment have good results. Risk factors for poor outcome are distant recurrence and more than three recurrence locations (99, 100).

1.5 BASIC RADIOBIOLOGY

The basics of radiobiology were retrieved from the textbook Basic Clinical Radiobiology published by Hodder Arnold (101).

The principle of combining radiotherapy and surgery has been shown to improve outcomes in the treatment of many types of cancer. The idea is that surgery effectively reduces the solid tumor mass while the removal of healthy tissue is limited. Radiotherapy decreases residual microscopic tumor deposits which the surgical procedure might have left behind. Preoperative radiotherapy can reduce tumor size and decrease the number of lymph node metastases, increasing the chance for an operation with tumor-free resection margins. Theoretically this would lead to a decreased risk of local recurrent disease and increased long-term survival.

The scientific definition of radiation is the transmission of energy in the form of waves or particles through space or in a medium. There are different types of radiation, for example: electromagnetic radiation, particle radiation and acoustic radiation (including sound). Radiation is either ionizing or non-ionizing depending on the level of energy of the particles. Ionizing radiation carries enough energy to break chemical bonds inside a cell and ionize atoms and molecules; this type of radiation has the potential to affect human cells. In clinical radiotherapy high energy electromagnetic radiation (x-rays) are used. The level of effect on

biologic tissue depends on the nature of the radiation and the type of tissue exposed. The linear energy transfer (LET) is measured in keV/µm and describes how much energy a particle transfers to the medium per traversed unit distance. A high LET will deposit its energy quickly in the tissue and will not penetrate deeply. Sparsely ionizing radiation includes x-rays and gamma rays which are low LET. High LET radiation includes energetic neutrons, protons, and heavy charged particles, also called densely ionizing radiations. The cut-off value between low and high LET is approximately 10 keV/µm. Radiation dose is measured as the amount of absorbed energy per mass of tissue, the unit is Joule/kg also known as Gray (Gy). 1 Joule/kg is equal to 1 Gy. In the treatment of most tumors including esophageal cancer low LET x-rays are used. Gamma rays are normally only used for head and neck cancers.

Cell damage from ionizing radiation is mainly caused by direct and indirect DNA damage. Parts of the radiation will interfere directly with DNA molecules. Recoil electrons will react with water and form hydroxyl radicals which in turn can react with target molecules and induce cell damage. The outcome for the cell can be immediate death through apoptosis or delayed death. It can also lose its ability for mitosis, either directly or after some divisions. Some cells will not respond to the radiation at all and some will adapt and become less sensitive to future radiation. The cell is most sensitive to ionizing radiation during the proliferation cycle, especially during the mitosis, which is a phase during the cell division. Tissues with high proliferation are more sensitive to radiation than tissues with a low proliferation rate. In a malignant tumor the cell proliferation is usually very high, making it a good target for radiation therapy. Concerning tumor cells, with high frequency of mitosis, cell death is defined as loss of reproductive ability. Cells that survive treatment without losing this ability are called clonogenic cells. The effects of radiation are immediate but the subsequent response in the cell can develop over hours or several years after exposure. Cells that survive radiation will repair their DNA in the first hours if no additional damage is caused. A cell survival curve describes the fraction of clonogenic cells in relationship to the absorbed dose. The shape of the curve differs depending on the type of radiation. A dose response curve plots the observed biological effect in an organ and the administered radiation dose. These curves depend on the radiation sensitivity of the cells and the proliferation rate. Skin, mucosa and intestinal epithelium are sensitive to radiation and are called early responders when examining a dose response curve. Late responders include, for example, bone marrow. The aim of radiotherapy is to kill the tumor without giving the surrounding tissues radiation doses that will lead to serious complications for the patient, the so-called therapeutic ratio. This is often described with two sigmoid curves of delivered dose and the tumor control probability (TCP) and the normal tissue complication probability (NTCP). Radiotherapy is normally delivered with a $TCP \geq 0.5$ and a $NTCP \leq 0.05$.

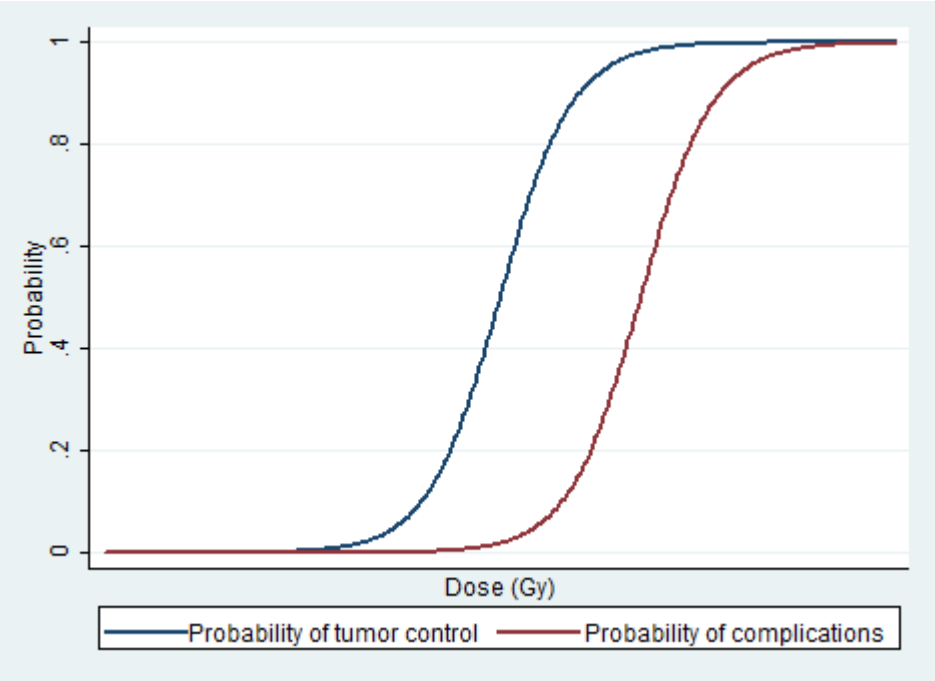


Figure 2. *The principle of the therapeutic ratio. The blue curve represents TCP and the red curve NTCP. The interval for treatment is between the curves.*

1.5.1 Fractionated radiotherapy

There are advantages with administrating radiotherapy in small repeated doses, so-called fractionated radiation, instead of one large dose. Fractionating gives an improved ratio of TCP and NTCP through five biological factors called the five Rs of radiotherapy.
1: Radiosensitivity varies in different tissues. 2: Repair of DNA will occur between treatments. 3: Repopulation of cells in the tissue between fractions. 4: Redistribution of cells in the cell cycle during treatment increases the cell death compared to one single high dose session. 5: Reoxygenation of hypoxic cells increases the radiosensitivity in the tissue. Healthy tissue is spared through repair of sublethal cell injuries and repopulation of the tissue. The tumor damage is increased through reoxygenation and redistribution between fractions.

1.5.2 Planning external beam radiotherapy

Radiotherapy is administered to the patient after careful planning of the radiation fields with the aim of giving the therapeutic dose to the tumor and at the same time limiting the dose, as much as possible, to vital organs. Today this is done with advanced three-dimensional computed technology. Computed tomography images of the tumor are used to identify the tumor and the critical surrounding organs. The gross tumor target volume (GTV) is the palpable, seen or imaged tumor. The clinical target volume (CTV) includes the GTV plus a surrounding margin of tissue at high risk of microscopic disease. Finally the planning target volume (PTV) is defined. PTV allows for uncertainties in the planning and accounts for the physiological movement of organs, for example due to breathing. It is crucial that the CTV is adequately treated to achieve a cure for the patients. The PTV is defined in every slice of the computed tomography and the organs at risk are also marked. The final treatment plan

includes dose distributions and dose-volume histograms of the PTV and the organs at risk. For each treatment session the patient is positioned with the help of tattooed marks on the skin and the radiotherapy is administered according to the treatment plan. Multiple treatment fields are used to give the full dose in the PTV with minimal damage to surrounding tissues.

1.6 NEOADJUVANT TREATMENT

With the ambition to improve long-term survival the trend in recent years has been to develop effective multimodal treatment including neoadjuvant chemotherapy (nCT), or combined neoadjuvant chemoradiotherapy (nCRT), followed by surgery. One concern is the risk of increased treatment-related morbidity with the addition of preoperative oncological treatment. Neoadjuvant treatment, with nCT or nCRT, followed by radical surgical resection is now the gold standard in curatively intended treatment. In RCTs both neoadjuvant regimens have been found to increase long-term survival compared to surgical resection alone (87, 102-110). Although there have been statistically significant survival benefits the difference is not very large compared to SA. In one retrospective study SA was shown to offer a 5-year survival rate of 59% for stage 0-II cancers, this number is higher than in many trials of neoadjuvant treatment (111). Regarding SCC in the western world, evidence of a beneficial effect on long-term survival is very well documented for nCRT, while effects are still unclear for nCT (102, 107, 112, 113). In Asia nCT is the standard treatment in esophageal SCC (114).
The postoperative morbidity and mortality after nCT has in most trials not been increased compared to SA. Postoperative complications after nCRT have in some trials been reported at similar numbers as for SA, while some show an increased postoperative risk (68, 86, 87, 115-119). The addition of preoperative radiotherapy kills malignant cells but the surrounding organs also receive radiation to some extent, although efforts are made to keep this to a minimum (120). Radiation pneumonitis, pericardial effusion and negative effects on blood vessels are a direct effect of radiotherapy and increase with the given dose and the volume of lung tissue not spared from doses over 5Gy (121, 122). The neoadjuvant radiation dose is most often 35-40 Gy. One study has shown increased local tumor control for patients receiving 41-50 Gy when compared to 36 Gy (123). Concerning nCT many different drug combinations, doses, and numbers of cycles of chemotherapy have been studied.
The patients who respond to the neoadjuvant treatment with complete histological response or downstaging of the tumor have been shown to have a statistically significant improved overall survival rate compared to non-responders and patients not receiving neoadjuvant treatment (116, 124-126). The number of lymph nodes resected is a quality measurement of the surgery in patients treated with SA. A high number of resected nodes have been associated with improved outcome. Neoadjuvant therapy decreases the number of resected lymph nodes, malignant as well as benign. This fact changes the way lymph node retrieval can be used as a marker for surgical quality (127).

Until now only two RCTs have been performed comparing nCT to nCRT directly (117, 128). Indirect comparisons of the treatments, i.e. comparing the results of a trial of nCT vs. SA with a trial of nCRT vs. SA, are common but can have some methodological problems (129).

For example assumptions of homogeneity of the included trials can introduce bias, and the comparisons of direct and indirect evidence can be inadequate. There are few observational studies with prospectively collected data based on a population within a well-defined population, evaluating the clinical practice, after the implementation of neoadjuvant treatment. Whenever a novel therapeutic concept is developed the question remains how effective it will be when applied in routine clinical practice and when offered to significant numbers of newly diagnosed patients. Until now large prospective cohort studies have been few and incomplete but have been unable to show an overall survival benefit as a result of the introduction of neoadjuvant treatment as compared to SA. The possible risk of increased perioperative morbidity and mortality has not been evaluated in large prospective cohorts. Patients with complete histological response have increased survival, compared to non-responders, and benefit from neoadjuvant treatment but today we are unable to identify these patients beforehand (130-132).

1.6.1 Cisplatin

For many years cisplatin has been a cornerstone of the treatment of esophageal cancer. It was developed during the 1960s and 1970s after it was discovered that the drug reduced the mass of sarcomas in rats (133). Cisplatin was approved for use in testicular and ovarian cancer in the United States in 1978 and in Europe in 1979. It is also used in the treatment of lung cancer, bladder cancer, cervical cancer, head and neck cancer, and lymphomas. The mechanism of action is binding of the platinum atom to DNA bases. This leads to crosslinking of the cell DNA which inhibits normal mitosis. The cell will then try to repair the DNA and if this doesn't work the cell will die through apoptosis. Many tumors are sensitive to cisplatin initially but develop resistance over time. Side effects include kidney damage, hearing loss, nausea and vomiting, and hemolytic anemia. Carboplatin and oxaliplatin belong to the same group of platinum-containing anti-cancer drugs as cisplatin and are also used in the treatment esophageal cancers.

1.6.2 5-fluorouracil

The finding that 5-fluorouracil, also known as 5-FU, inhibited tumor growth in mice was described by Heidelberger and colleagues in 1957 (134). 5-FU is a commonly used drug, either as a single drug or administered together with other chemotherapy drugs in the treatment of, for example; breast cancer, head and neck cancers, anal cancer, and colorectal cancer. 5-FU is a so-called anti metabolite and it has more than one mechanism of action. It is a thymidylate synthase inhibitor which interrupts the intracellular synthesis of the nucleoside thymidine, which leads to cell death through apoptosis. It is also incorporated in the RNA molecule and can inhibit the intracellular production of RNA. Common side effects are leukopenia, thrombocytopenia, nausea and vomiting, and stomatitis. The risk of neurotoxicity increases with the administered dose. Cardiotoxicity is a known but uncommon side effect. The risk is higher in patients with previous cardiovascular disease. Patients with the metabolic disorder dihydropyrimidine dehydrogenase deficiency can develop life-threatening toxicity if exposed to 5-FU.

1.6.3 Epirubicin

Epirubicin is an anthracycline drug which was first approved for use in node-positive breast cancer. The first trial in humans was published in 1980 by Bonfante and colleagues (135). It can also be used in gastric cancer treatment and for intravesical administration in superficial vesical cancer. The mechanism of action is not fully understood. The drug binds to the DNA molecule which inhibits DNA and RNA synthesis and triggers DNA cleavage, resulting in cell death. The drug also binds to cell membranes and plasma proteins which may increase the cytotoxic effects. Side effects that occur are leukopenia, and granulocytopenia with subsequent infections, anorexia, dehydration, and mucositis. In the MAGIC trial perioperative administration of cisplatin, 5-FU and epirubicin increased long-term survival for patients with gastric or esophageal AC.

1.6.4 Paclitaxel

Paclitaxel is a member of the taxane drug class and is made from the bark of the rare Pacific yew tree. It was discovered in 1962. A semi-synthetic and more potent analogue of the chemotherapeutic is docetaxel. The drug inhibits mitotic cell division through interference with normal breakdown of microtubules in the cell. It is used in the treatment of several cancer types for example; breast, lung, prostate, ovarian, and bladder tumors. Common side effects include; neutropenic infections, muscle pain, and hair loss. The CROSS regimen nCRT for esophageal cancer includes paclitaxel and carboplatin, in combination with concurrent radiotherapy with a total dose of 41.4 Gy (87).

1.6.5 Tumor regression grade

Complete histological tumor regression after neoadjuvant treatment is associated with improved survival rates compared to partial or no response (124, 136, 137). Tumor regression has been shown to be associated with downstaging of the tumor and the interobserver agreement between pathologists has been shown to be good (138, 139). With the use of PET-CT it may be possible to assess the individual patient's early response to neoadjuvant treatment (140-143). In the future the combination of molecular tumor markers, PET-CT, and endoscopic evaluation with ultrasound can hopefully be used to evaluate the patient's response (144), and select which patients benefit from completing neoadjuvant therapy and which ones may benefit from early interruption and immediate surgery (145). Tumor regression grade (TRG) is assessed in the surgical specimen by the pathologist and is based on the quota of tumor cells and fibrosis, the lymph node status is not included. The TRG can be graded according to several different grading systems (131, 146). Chirieac and colleagues described a four-grade scale where TRG 1 represents pathological complete response with no remaining tumor cells; TRG 2 represents 1–10% tumor cells; TRG 3, 11–50% tumor cells; and TRG 4, >50% tumor cells (124). There is an ongoing study of the accuracy of determining residual tumor with endoscopy and endoscopic ultrasound in patients who respond to treatment with complete histological response (147). The hypothesis is that it may be possible to abstain from surgery in patients with complete response to neoadjuvant treatment and instead follow them with regular endoscopic and radiological evaluations.

Patients with none or partial response will undergo surgery after the neoadjuvant therapy is concluded. Esophagectomy can later be performed in patients with local recurrent disease The optimal time between the end of neoadjuvant treatment and surgery has yet to be determined. A waiting period of 4-6 weeks has often been used but some data indicate that a prolonged wait of 10-12 weeks could increase the TRG (148). Complete histological tumor response has been shown to be a prognostic factor for long-term survival, and combined with data regarding short-term survival it can be used to evaluate the effect of neoadjuvant treatment of esophageal carcinoma (149-151).

1.6.6 Neoadjuvant chemotherapy vs. surgery alone

Neoadjuvant chemotherapy for resectable esophageal cancer has been studied since the 1980s; studies have mostly compared different neoadjuvant treatments to SA without supplementary oncological treatment, which has been the standard regimen for many years. nCT has been found, in clinical trials, to increase survival without notably increasing the risk of postoperative morbidity or mortality when compared to SA (68, 103-105). The results are, however, heterogeneous and far from complete but a statistically significantly effect on overall survival has been observed in patients with AC, while the data are more ambiguous for SCC (103, 107, 125, 152-155). In Japan nCT is the standard treatment since the Japan Clinical Oncology Group (JCOG) 9204 trial and the 9907 trial showed increased survival rate for patients with SCC compared to SA (80, 93).

Rates of postoperative morbidity and mortality were similar between groups in most studies. Alderson and colleagues compared two cycles of cisplatin/5-FU to 4 cycles of epirubicin/ cisplatin/capecitabine. Capecitabine is an orally administered prodrug which converts enzymatically to 5-FU in the body. The longer chemotherapy resulted in increased tumor regression grade, and prolonged disease-free survival but overall survival was not improved and the treatment-related toxicity was higher (156). Further studies are needed to improve the efficacy of the neoadjuvant chemotherapy.

Table 1. *Selected randomized clinical trials comparing neoadjuvant chemotherapy to surgery alone.*

Study	Patients	Oncological treatment	Results
Roth (157) J Thorac Cardiovasc Surg 1988.	39 patients, 19 had peri-operative chemo. 20 had SA.	One cycle of neoadjuvant cisplatin and bleomycin, four cycles of vindesine. Repeated postoperatively.	Increased survival for responders in the chemo-group, median over 20 months vs. 8.6 months in the surgery group. No difference in adverse events.
Nygaard (158) World J Surg 1992.	186 patients with SCC divided into four groups; SA, nRT, nCRT and nCT.	Two neoadjuvant cycles of cisplatin and bleomycin.	The study showed no increase in survival comparing the nCT group to the SA group.
Schlag (159) Arch Surg 1992.	46 patients with SCC; 22 to nCT and 24 to SA.	Three neoadjuvant cycles of fluorouracil and cisplatin.	Increased survival for responders to nCT (median 13 months vs. 5 months for non-responders). No difference in overall survival between groups. More adverse events in nCT group.
Law (160) J Thorac Cardiov Surg 1997.	147 patients with SCC. 74 received nCT and 73 SA.	Two neoadjuvant cycles of cisplatin and 5-fluoracil.	Median survival was 16.8 vs. 13 months, p=0.17. No difference in postoperative mortality.
Kelsen (152) N Engl J Med 1998.	440 patients, 236 with ADC and 204 with SCC. 213 received peri-operative CT and 227 SA.	Three cycles neoadjuvant cisplatin and fluorouracil plus two adjuvant cycles.	Median survival was 14.9 months in the nCT group and 16.1 months in SA p=0.53. No difference between ADC and SCC. No difference in postoperative morbidity and mortality.
Baba (161) Dis. of the Esophagus 2000.	47 patients with SCC.	Two neoadjuvant cycles of cisplatin and 5-FU and leucovirin.	No increase in survival comparing the nCT group to the SA group. No statistically significant difference in complications.
Ancona (125) Cancer 2001.	96 patients with SCC 48 had nCT and 48 had SA.	Two or three neoadjuvant cycles of cisplatin and 5-fluorouracil.	No difference in overall survival. Patients that responded to chemotherapy had a 3-year survival rate of 74% vs. 24% for non-responders and 5-year survival rate of 60% vs. 12% p=0.0002.

Medical research council (104) Lancet 2002.	The OEO2 trial. 802 patients, nCT: 400 and SA: 402.	Two neoadjuvant cycles of cisplatin and 5- fluorouracil. Preoperative radiation optional.	Overall survival was better in the nCT group HR for death in nCRT 0·79 (95% CI 0·67–0·93) p=0.004. Median survival 16.8 vs. 13.3 months. No difference in postoperative morbidity or mortality.
Cunningham (103) N Engl J Med. 2006.	The MAGIC trial. 503 patients with gastric or esophageal AC randomly assigned to nCT (n=250) or SA (n=253).	Three cycles of epirubicin, cisplatin and fluorouracil plus three adjuvant cycles.	Hazard ratio for death after 4 years was 0.75 (95% CI, 0.60 to 0.93) p=0.009; 5-year survival rate, 36% vs. 23%. No difference in complications.
Boonstra (153) BMC Cancer 2011.	169 patients with SCC in esophagus. 85 nCT and 84 SA.	Two to four cycles of cisplatin and etoposide.	5-year survival rate 26% vs. 17%; HR for death: 0.71 (95% CI, 0.51 to 0.98), p=0.03. Pulmonary complications 23% after nCT and 10% after SA, p=0.048.
Ychou (105) J Clin Oncology 2011.	224 patients with ADC in esophagus or stomach.113 nCT and 111 SA.	Two or three cycles of cisplatin and 5-fluorouracil plus three or four adjuvant cycles.	5-year survival rate 38% vs. 24%; HR for death: 0.69 (95% CI, 0.50 to 0.95), p=0.02. No difference in postoperative morbidity.

1.6.7 Neoadjuvant chemoradiotherapy vs. surgery alone

The first trials investigating nCRT in the treatment of esophageal cancer were performed in the 1990s. Results show better overall survival after nCRT compared to SA for both AC and SCC although the difference is not very large. Perioperative morbidity and mortality has not been significantly elevated in most trials, however some studies do show an increased postoperative risk compared to SA (68, 106, 162-164). nCRT is currently the gold standard treatment for esophageal AC and SCC in many countries including Sweden. In Japan nCRT has not been implemented as described above. Several trials have been performed to investigate which nCRT regimen is the most effective and which patient category benefits most from the treatment (165). Marriette and colleagues showed that nCRT increases the risk of postoperative complications without improving survival for patients with stage I-II esophageal cancer (118). Induction chemotherapy before nCRT was investigated by Ajani and colleagues without showing a survival benefit (166). Two studies have shown an increased risk for anastomotic leakage if the anastomosis is placed within a preoperative radiation field (167, 168).

Table 2. *Selected randomized clinical trials comparing neoadjuvant chemoradiotherapy to surgery alone.*

Study	Patients	Oncological treatment	Results
Nygaard (158) World J Surg 1992.	186 patients with SCC divided into four groups; SA, nRT, nCRT and nCT.	Two neo-adjuvant cycles of cisplatin and bleomycin and 35 Gy radiotherapy.	Significantly increased 5-year survival rate for patients receiving neoadjuvant radiotherapy.
Le Prise (169) Cancer 1994.	86 patients with SCC randomized to nCRT (n=41) or SA (n=45).	Two neo-adjuvant cycles of cisplatin and 5- fluorouracil and 20 Gy radiotherapy.	One-year survival rate of 47% in both groups. No difference in postoperative mortality 8.5% after nCRT vs. 7% after SA.
Apinop (170) Hepato-gastroenterology. 1994.	69 patients with SCC randomized to SA or nCRT.	Two neo-adjuvant cycles of cisplatin and 5- fluorouracil and 40 Gy radiotherapy.	Slight increase in survival comparing the nCRT group to the SA group but not significant. No difference in complications.
Walsh (171) N Engl J Med. 1996.	113 patients randomized to nCRT (n=58) or SA (n=55).	Two neo-adjuvant cycles of cisplatin and 5- fluorouracil and 40 Gy radiotherapy.	Median survival was 16 months after nCRT and 11 months for SA, p=0.01. No difference in postoperative morbidity.
Bosset (116) N Engl J Med. 1997.	282 patients with SCC were randomized to nCRT (n=143) or SA (n=139).	Two neo-adjuvant cycles of cisplatin and 18.5 Gy radiotherapy.	Median survival was 18.6 months in both groups. nCRT group had longer disease free survival, p=0.003, however postoperative mortality was 17% vs. 5% for SA, p=0.012.
Urba (172) J Clin Onc. 2001.	100 patients with SCC or AC were randomized to nCRT or SA.	Three neo-adjuvant cycles of cisplatin and vinblastine, two cycles of 5-FU and 45 Gy radiotherapy.	Median survival was 17.6 months in the SA group and 16.9 months after nCRT. No statistically significant difference in frequency of complications.
Lee (173) Annals of Onc 2004.	101 patients with SCC, nCRT (n=51) or SA (n=50).	Two neo-adjuvant cycles of cisplatin, 5-FU, and 45.6 Gy concurrent radiotherapy.	Median overall survival: 27.3 months in SA and 28.2 months in nCRT, p=0.69. No difference in postoperative morbidity or mortality.
Burmeister (86) Lancet Onc 2005.	256 patients with ADC and SCC randomly assigned to nCRT (n=128) or SA (n=128).	One neo-adjuvant cycle of cisplatin and fluoracil and 35 Gy radio-therapy.	No difference in overall survival but increased rate of R0 resections p=0.0002 and fewer lymph node metastasis p=0.003.Increased disease free survival for SCC vs. ADC. No difference in postoperative complications.

Natsugoe (174) Dis of the Esoph. 2006.	45 patients with SCC randomized to nCRT (n=22) or SA (n=23).	4 cycles of Cisplatin, 5-FU, 40 Gy concurrent radiotherapy.	Five-year survival rate: 57% after nCRT and 41% after SA, p=0.58.
Cao (175) Dis of the Esoph. 2009.	473 patients with SCC randomized to nRT (n=118), nCT (n=119), nCRT (n=118) or SA (n=118).	Cisplatin, 5-Fluorouracil, Mitomycin week 1+2, radiotherapy total dose 40 Gy week 3-6.	Three-year survival rate: 69.49% nRT, 73.73% nCRT vs. 53.38% SA, p<0.05. nCT 57.1% no significant difference compared to SA.
van Hagen (87) N Engl J Med. 2012.	The CROSS trial. 366 patients with ADC or SCC randomized to nCRT (n=178) and SA (n=188).	Carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy of 41.4 Gy.	Median survival was 49.4 months in the nCRT group vs. 24.0 months in the SA group. Hazard ratio for death in the nCRT group was, 0.657 (95% CI 0.495 to 0.871), p=0.003. No difference in postoperative complications.
Marriette (118) J Clin Onc. 2014.	195 patients with stage I or II esophageal cancer, randomized to SA (n=97) and nCRT (n=98), 70% SCC and 30% ADC.	Two neo-adjuvant cycles of cisplatin and 5- fluorouracil and 45 Gy radiotherapy.	No difference in overall survival but increased rate of postoperative mortality of 11.1% nCRT vs. 3.4% SA, p=0.049.

1.6.8 Neoadjuvant chemotherapy vs. neoadjuvant chemoradiotherapy followed by resection

Previous to our study two randomized controlled trials have been performed comparing nCRT to nCT. Both have a limited sample size and it is still unclear which treatment strategy to recommend. Several studies have, in indirect comparisons, shown a higher rate of complete histological response and R0 resections and a slightly better long-term outcome for patients who receive nCRT compared to nCT (102, 176, 177). Neoadjuvant radiotherapy in addition to chemotherapy increases local tumor control but some studies also show an increased risk of postoperative complications, especially heart and lung problems possibly due to the distribution of the radiation field. nCRT might give a higher risk of postoperative complications in patients with squamous cell carcinomas than adenocarcinomas (68, 128). The interpretations of these analyses are uncertain due to the heterogeneous design of the included studies and in particular due to the fact that the studies that have compared nCRT to nCT have a limited sample size (178).

Table 3. *Randomized clinical trials comparing nCT to nCRT.*

Study	Patients	Oncological treatment	Results
Stahl (117) J Clin Oncology 2009.	126 patients with ADC were randomized to nCRT (n=60) or nCT (n=59).	Two and a half courses of cisplatin, fluorouracil, and leucovorin in the nCRT group two courses with the addition of 30 Gy concurrent radiotherapy, 2 Gy fractions.	Three-year survival rate was 47.4% in the nCRT group vs.27.7% in the nCT group, p=0.07, HR for death in the nCRT group was 0.67 (95% CI, 0.41 to 1.07). Postoperative mortality was increased in the nCRT group; 10.2% v 3.8% p=0.26.
Burmeister (128) Eur J Cancer 2011.	75 patients with ADC randomized to nCRT (n=39) or nCT (n=36).	Two neoadjuvant cycles of cisplatin and 5-fluorouracil. In the nCRT group with the addition of concurrent radiotherapy of 35 Gy 2.3 Gy fractions.	No difference in overall survival but increased rate of histological response 31% vs 8%, p=0.01, and R0 resection 100% vs. 89%, p=0.04.

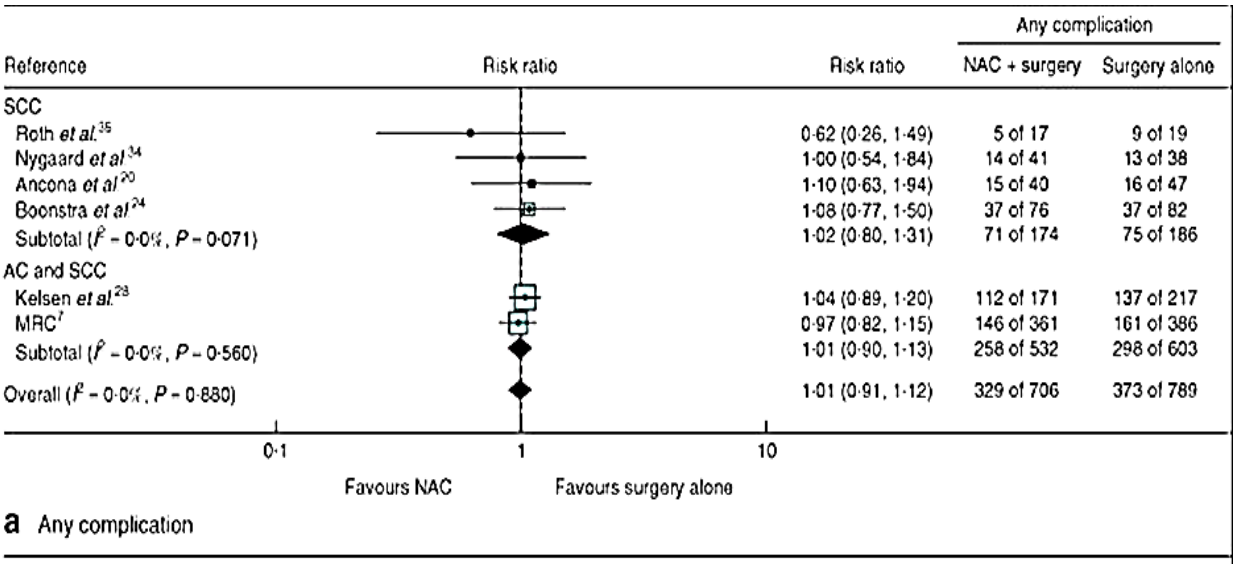
1.6.9 Meta-analyses of nCRT and nCT

Meta-analyses of nCRT and nCT for esophageal cancer have shown survival benefits for both treatments with slightly better outcomes for patients receiving nCRT (102, 107, 179-182). The improved outcome was seen for both AC and SCC and the anticipated increased risk for perioperative mortality was not shown. There was however heterogeneity in the included trials concerning tumor type, tumor location, chemotherapy and radiotherapy regimens and preoperative staging.

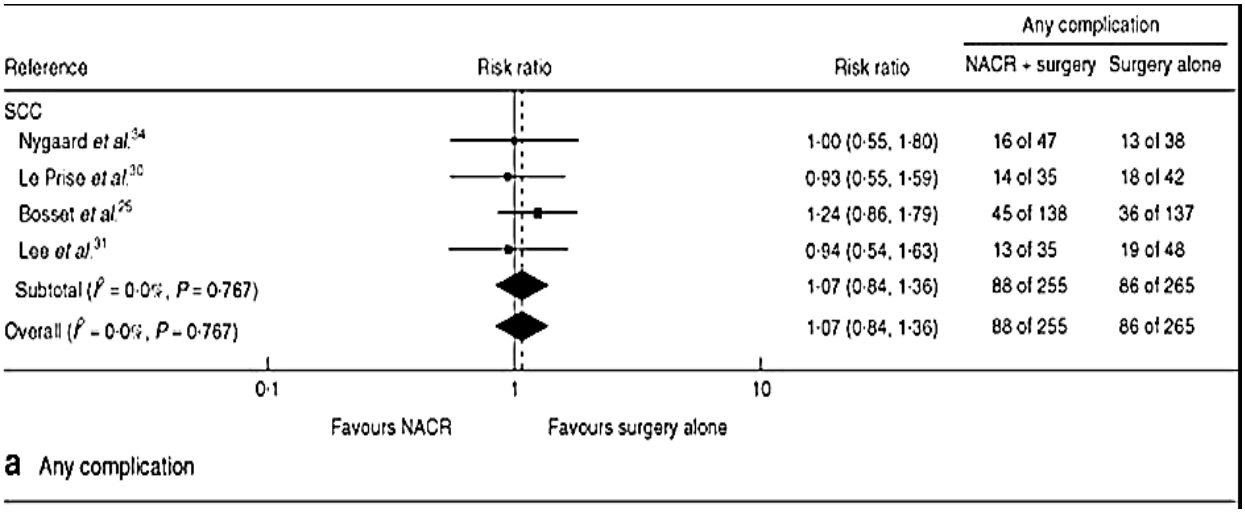
Our group performed a meta-analysis investigating postoperative morbidity and perioperative mortality after nCRT, nCT and SA (68). The analysis included 23 trials, 7 compared nCT to SA, and 11 compared nCRT to SA. The analysis did not show any increased risk for postoperative complication, cardiac complication, respiratory complication, anastomotic leakage, 30-day mortality, total postoperative mortality or treatment-related mortality after nCT compared directly with SA. For patients with SCC, there was a statistically non-significant trend of an increased risk of respiratory complications after nCT compared to SA (RR 1.46, 95 per cent CI 0.92 – 2.30, p=0.105).

nCRT did not increase the overall postoperative risk compared to SA, but patients with SCC did have a statistically significant increased risk of total postoperative mortality; risk ratio: 1.95 (95% CI 1.06-3.60, p=0.032). Treatment related mortality was also increased in this group; risk ratio: 1.97 (95% CI 1.07-3.64, p=0.030). This was not seen for patients with AC. Direct comparison of nCT and nCRT did not show any significant difference.

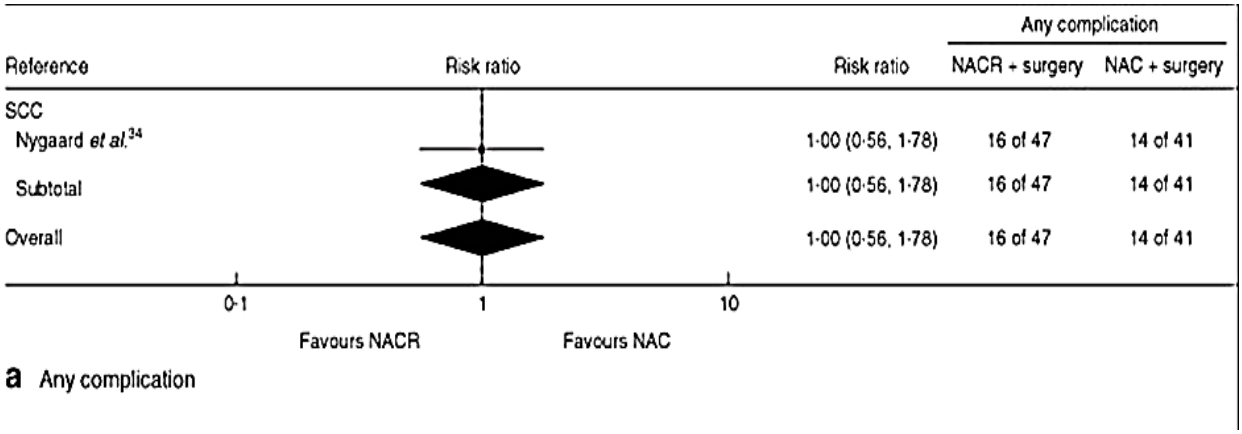
Figure 3. *Forest plots from the meta-analysis (68).*



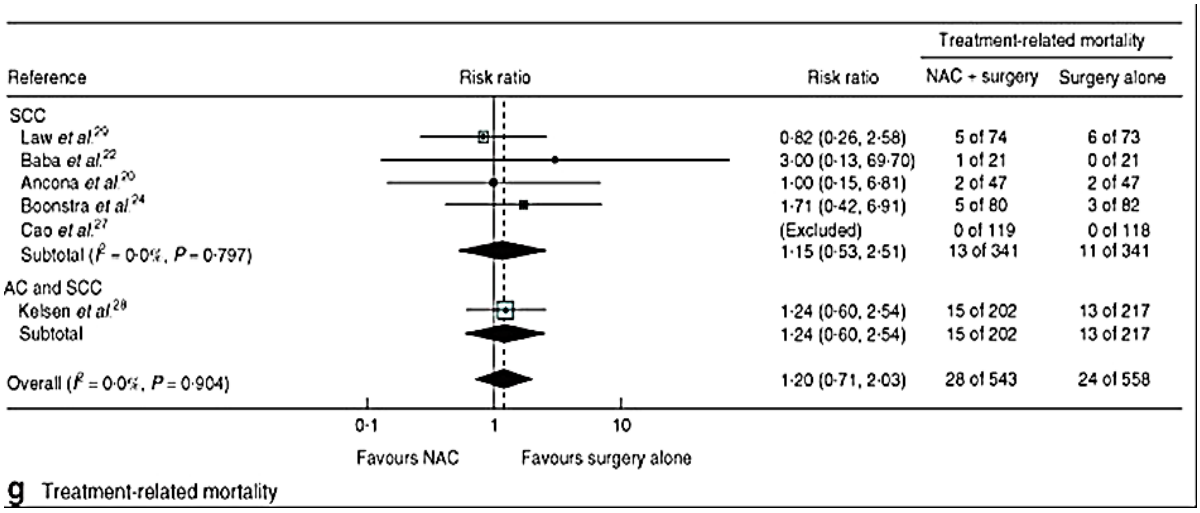
Forest plot displaying the risk ratios for any postoperative complication after nCT compared to SA. NAC is an abbreviation for nCT.



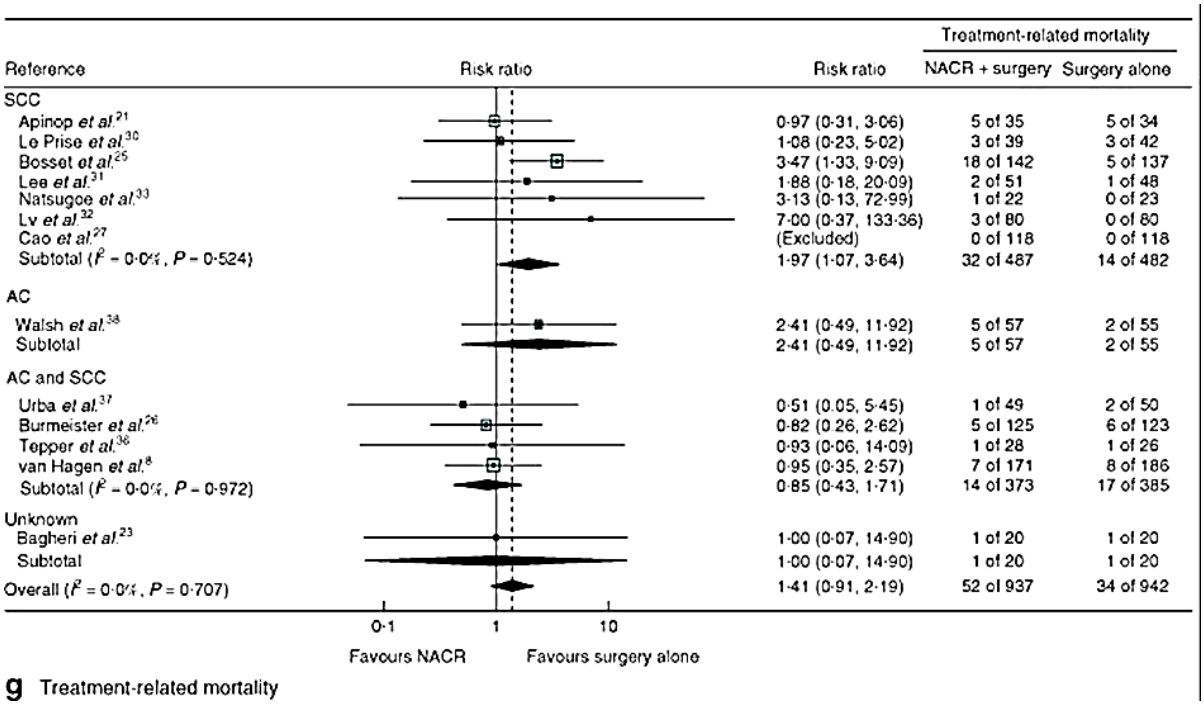
Any complication comparing nCRT and SA. NACR is an abbreviation for nCRT.



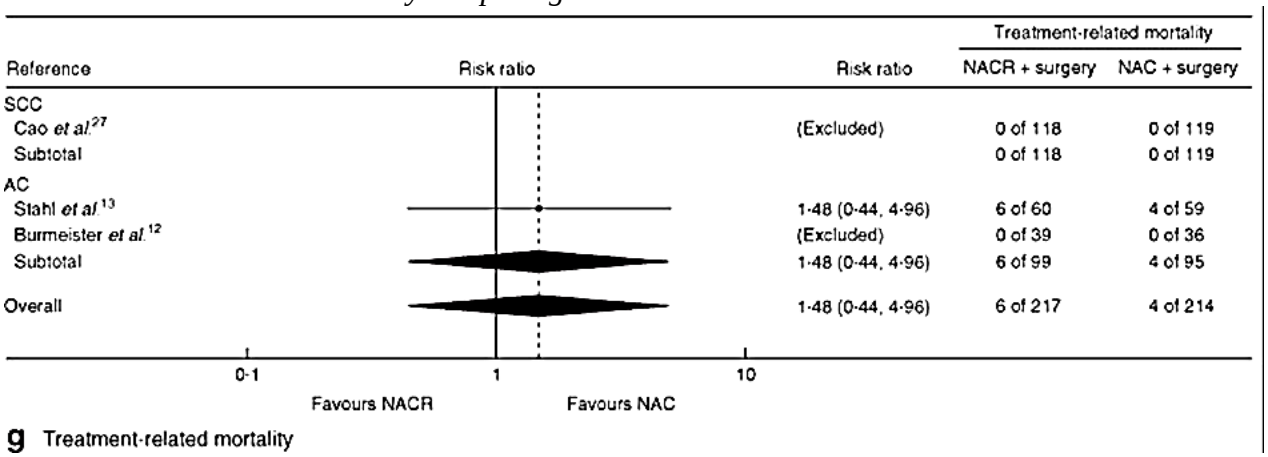
Risk ratios for any complication after nCRT compared to nCT.



Total treatment-related mortality after nCT vs. SA.



Total treatment-related mortality comparing nCRT and SA.



Direct comparison of treatment-related mortality after nCRT and nCT.

2 AIMS

The aims of this thesis were:

To increase the knowledge about morbidity and mortality after neoadjuvant chemotherapy and chemoradiotherapy followed by esophagectomy.

To compare the tumor regression grade after neoadjuvant chemotherapy compared to neoadjuvant chemoradiotherapy in a randomized controlled trial.

To evaluate if neoadjuvant chemoradiotherapy increases the chance for overall survival compared to chemotherapy.

To examine the effects of the implemented neoadjuvant treatment strategies in Sweden using population-based registry data.

To estimate the magnitude of radiation exposure at the predicted site of the anastomosis in the gastric fundus.

To investigate the effect of neoadjuvant chemoradiotherapy on the frequency, and severity of cervical anastomotic complications.

3 SUBJECTS AND METHODS

3.1 THE NEORES TRIAL

Papers I and III are based on the Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Esophagus and Gastric Cardia (NeoRes) trial, which was performed in Norway and Sweden during the period 2006–2013. The purpose of the trial was to clarify if neoadjuvant chemoradiotherapy gives a higher degree of complete histological response than neoadjuvant chemotherapy in patients undergoing treatment for cancer of the esophagus or gastro-esophageal junction.

3.1.1 Setting

Participating centers in Norway were the Oslo University Hospital, St Olav's University Hospital, Trondheim, and Haukeland University Hospital, Bergen; and in Sweden, the Norrland University Hospital, Umeå, Karlstad Central Hospital, Örebro University Hospital, Sahlgrenska University Hospital, Göteborg, Mälarsjukhuset, Eskilstuna, and Karolinska University Hospital, Stockholm.

3.1.2 Eligibility

Patients with histologically confirmed SCC or AC of the esophagus or GEJ (including Siewert types I and II (183)) who were eligible for curative treatment with surgical resection were enrolled. Cervical cancers were required to be resectable without laryngectomy. Study participants had to be no more than 75 years of age, fit for esophagectomy, and have an Eastern Cooperative Oncology Group (ECOG) performance score (184) of 0 or 1. Adequate renal function defined as having normal serum creatinine levels and/or calculated glomerular filtration rate > 60 ml/min. Adequate haematological values: WBC $>3x10^9$/litre, and platelets $>100x10^9$/litre. Using the Union for International Cancer Control (UICC) TNM-6, patients with T1–3, any N (with the exception of T1N0) without evidence of distant metastases, were eligible (185-187). Comorbidities in the form of significant heart disease within the last year or a concurrent malignancy within the last five years constituted grounds for exclusion.

3.1.3 Staging

The clinical tumor and lymph node stage was assessed by upper gastrointestinal endoscopy and by a CT of the upper abdomen and chest. The use of FDG-PET and endoscopic ultrasonography was optional.

3.1.4 Study design and Statistical analysis

The study was designed as a phase-II randomized clinical trial comparing two neoadjuvant treatment regimens with complete histological response in the surgical specimen as the primary endpoint variable. The sample-size calculation was based on the intention of showing a difference in complete histological response of 15% between treatment arms with a power of 80%, which required 172 patients.

3.1.5 Randomization and masking

Patients were stratified by histological tumor type and randomized independently through the use of computerized software at the Regional Oncological Center in Stockholm. The allocation sequence was concealed to all investigators.

3.1.6 Ethics

All patients signed a written informed-consent form. The study was approved by the Research Ethics Committees in Sweden, (registration numbers 2006/738-32 and 2008-403-32), and Norway (Helseregion Midt-Norge registration number 4.2008.416). The full study protocol was registered in the Clinical Trials Database (https://clinicaltrials.gov; registration number NCT01362127).

3.1.7 Chemotherapy

Treatment had to be started within two weeks of randomization. Three cycles of cisplatin, 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hours, day 1-5 were given. Each cycle lasted 21 days. In case of hearing impairment, tinnitus or deterioration of renal function cisplatin was replaced by carboplatin, AUC 5 (patients with squamous cell carcinoma) or oxaliplatin, 130 mg/m^2 (patients with adenocarcinoma).

3.1.8 Radiotherapy

In patients randomized to receive chemoradiotherapy 40 Gy was given (2 Gy once daily in 20 fractions, 5 days a week) with a photon beam linear accelerator concomitant with chemotherapy cycle 2 and 3. A three-dimensional dose planning system was used. For tumors located mainly above the carina, the caudal border of the CTV was 5 cm below the tumor and the supraclavicular nodes defined the upper border. For tumors located mainly below the carina the cranial border of the CTV was 5 cm cranial to the tumor and the lower border was defined by the coeliac lymph nodes. In the lateral, anterior and posterior directions the CTV should embrace the gross tumor volume and para-esophageal area with a margin of 1 cm, although respecting anatomical barriers such as pleura, pericardium and bone. The planning target volume was carried out according to local routines. The dose to the lungs exceeding 20 Gy was kept as low as possible not exceeding 1/3 of the lung volume. The volume of the heart that received ≥30 Gy was kept to a minimum.

3.1.9 Surgery

Patients were scheduled to undergo resection four to six weeks after having completed neoadjuvant treatment. The protocol required two-field lymphadenectomy, and the recommended procedure was esophagectomy with intrathoracic anastomosis through a laparotomy and a right-sided thoracotomy (Ivor Lewis procedure). A three-stage resection, with a right-sided thoracotomy, laparotomy, and cervical incision (McKeown procedure) was recommended for tumors in the middle and upper thirds of the esophagus. Other procedures were accepted in cases where the individual surgeon considered it appropriate, such as transhiatal esophagectomy, only employing laparotomy and a cervical incision for distal

esophageal and junctional cancers, or total gastrectomy for junctional tumors classified as Siewert type II (Table 1).

3.1.10 Monitoring

During the neoadjuvant therapy, patients were reviewed at least every third week. During radiotherapy patients were reviewed weekly. Adverse events were scored according to the NCI CTCAE v. 3.0 scale. Follow-up examinations were conducted every three months for the first two years after surgery and then every six months thereafter. During follow-up, radiological examinations were performed on suspicion of recurrence.

3.1.11 Definitions of outcomes

The primary endpoint was histological complete response in the primary tumor. Secondary endpoints were overall survival (time from randomization to death by any cause), progression-free survival, site of recurrence, R0 resection rate, number of lymph-node metastases, and toxicity of treatment. Progression was defined as a locoregional or distant recurrence, death from any cause, or disseminated disease before surgery. Patients with macroscopically unresectable tumors at surgery were regarded as having progression at the time of surgery. Patients with microscopic residual tumors (R1) were regarded as having progressed when there were clinical signs of disease progression. The resection was considered to be radical (R0) if there were no tumor cells within 1 mm of any resection margin (34, 188). Both longitudinal and circumferential resections margins were assessed.

3.2 PAPER I

3.2.1 Study design

Short-term follow-up of the first 90 days after surgery in the randomized clinical trial NeoRes was performed to compare the incidence and severity of postoperative complications after esophagectomy for carcinoma of the esophagus or GEJ.

3.2.2 Definitions of outcomes

Detailed data about perioperative complications and interventions during the whole length of stay were collected in the case record forms.

Anastomotic leakage was assessed using CT scans with an oral water-soluble contrast medium, and any uncertainty was followed up with an endoscopy for confirmation.

Surgical complications were defined as complications directly caused by the surgery, for example anastomotic leakage, conduit necrosis, bleeding, chylothorax, and recurrent laryngeal nerve paralysis.

Nonsurgical complications included cardiovascular events and arrhythmias requiring treatment, thromboembolism, respiratory failure, and infections not related to the operation field.

Clavien-Dindo Score: The severity of complications was classified according to the Clavien-Dindo (CD) scoring system for postoperative complications. CD grade I is a complication not requiring any medical treatment. CD grade II requires pharmaceutical treatment or blood transfusion. CD grade IIIa requires surgical, endoscopic, or radiological intervention without general anesthesia, for example insertion of a drain or gastroscopy. CD grade IIIb requires intervention in general anesthesia, for example re-operation. CD grade IVa is defined as a life-threatening complication leading to single-organ dysfunction. CD grade IVb is defined as a life-threatening complication with multi-organ dysfunction. CD V is death of a patient caused by a complication of the treatment (66, 189, 190). The comprehensive complication index (CCI) including all postoperative complications giving patients an index between 0-100 was also used (191).

3.2.3 Statistical analysis

Data were analysed according to the intention-to-treat principle. Comparisons between the two groups were done with the Chi-square test and Fisher's exact test. Logistic regression was used to compare various complication rates between the two groups, while controlling for potential confounding effects of covariates (age, gender, WHO performance grade, T-stage, tumor location). STATA/IC 13.1 software (StataCorp. LP, College Station, Texas, USA) was used for all statistical analyses.

3.3 PAPER II

3.3.1 Study design

The study was designed as a retrospective cohort study of all patients with cancer of the esophagus or gastro-esophageal junction undergoing esophagectomy operations and reconstructed with a gastric pull-up and cervical anastomosis at the Karolinska University Hospital in Stockholm 2007-2014. The aims of this study were first to estimate the magnitude of radiation exposure at the predicted site of the anastomosis in the gastric fundus, induced by nCRT within a standardized protocol, and secondly to assess whether nCRT affected the incidence or severity of cervical anastomotic complications. A non-irradiated group (non-RT) including patients with nCT and SA was compared to an irradiated group who had received nCRT. All esophagectomies with neck anastomosis were extracted from the hospital surgical planning system, ORBIT, and cross-matched for validation with data on all esophageal operations at the hospital from the electronic patient chart system TakeCare. Data regarding surgical procedures, neoadjuvant therapy, and potential confounding variables as well as outcomes were manually extracted from the patient charts in TakeCare. Comorbidity was calculated using the Charlson Comorbidity Index (192).

3.3.2 Neoadjuvant treatment

Radiotherapy (RT) was administered to target volumes defined in agreement with ICRU Report 50. All planning was to be carried out with a CT-based three-dimensional planning system with inhomogeneity correction. Patients were positioned for treatment according to tattooed marks on the skin and radiological landmarks in the vertebral column. The intended standard treatment dose was 40 Gy total to the tumor, given in 2 Gy fractions, 5 days/week over 4 weeks. GTV was defined as primary esophageal tumor and gross lymph node metastases. CTV included GTV and local subclinical disease. For tumors located at or above the level of the carina, the caudal border of CTV was 5 cm below diagnosed tumor and the supraclavicular nodes defined the cranial border. For tumors located mainly below the carina level, the cranial border of CTV included 5 cm of radiographically uninvolved esophagus and the coeliac lymph nodes defining the caudal border down to upper part of L1, while the coeliac lymph nodes were included in the target volume, at the same time defining the caudal border, down to the upper part of L1. In lateral, anterior and posterior directions, CTV should encompass GTV and para-esophageal area with a margin of 1 cm, but not including anatomical barriers such as pleura, pericardium or bone. Appropriate margins were added to the CTV to take into account the effects of organ and patient movements and inaccuracies in beam and patient set-up in order to ensure that the prescribed dose is actually absorbed in the CTV. All patients were followed weekly during radiotherapy.

3.3.3 Radiation exposure assessment

Detailed anatomical data on dose planning of radiation were extracted directly from the dose plan in the Varian treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) for irradiated patients. For each of these patients, two esophageal surgeons (FK

and MN) blinded to patient identity and outcome, estimated the likely site of cervical anastomosis on the fundus part of the stomach corresponding to the future gastric conduit, using the dose planning CT. The planned radiation dose to this site was recorded for each patient.

3.3.4 Surgery

In most patients operated on for esophageal or junctional carcinoma at the Karolinska University Hospital during the study period, an Ivor Lewis procedure with an intrathoracic anastomosis was used. The patients included in the study, comprising only the proportion in which a cervical anastomosis was employed, were operated on with other approaches due to tumor factors, such as location and stage, and patient factors such as comorbidity, age and previous surgery. Transhiatal esophagectomy was used primarily in junctional cancers in patients with severe, especially pulmonary, comorbidity. Open three-field McKeown esophagectomy was used mainly in tumors located in the mid and upper esophagus. Minimally invasive techniques, three-stage laparoscopic and thoracoscopic, as well as the hybrid approaches combining laparotomy, thoracoscopy and neck incision or laparoscopy, thoracotomy, and neck incision, were used during the last years of the study period due to the shift to minimally invasive techniques implemented at the department. Before the conduit was created, the right gastric artery was identified and the branches of the artery to the distal part of the antrum were preserved. A gastric tube about 4 cm wide along the major curvature side of the stomach was completed by using a linear stapler applied along the contralateral side. The anastomotic technique was standardized and was the same in all the surgical approaches using cervical anastomosis where each anastomosis was constructed by use of interrupted monofilament, absorbable, single layer, 4-0 sutures end to side against a longitudinal incision of the greater curvature of the gastric conduit.

3.3.5 Definitions of outcomes

Postoperative outcome was registered during the full length of stay after surgery and during any readmission due to postoperative complications.

Anastomotic complications: The occurrence of an anastomotic complication was defined as anastomotic leakage or gastric conduit necrosis diagnosed by CT with intraluminal contrast medium, endoscopy, or both.

Surgical complications: Surgical complications were defined as all complications directly related to the surgical field, including anastomotic complications, surgical site infections, thoracic duct injury, postoperative hemorrhage and recurrent laryngeal nerve paralysis.

Nonsurgical complications: Nonsurgical complications comprised cardiovascular events and arrhythmias requiring treatment, thromboembolism, respiratory failure requiring invasive or non-invasive intervention, and serious infections not related to the surgical field such as sepsis and pneumonia.

Overall postoperative morbidity: The overall postoperative morbidity included both surgical and non-surgical complications.

Severity of complications: The severity of the anastomotic complications was classified using

the Clavien-Dindo score (189).

Ninety-day mortality: The 90-day mortality was defined as death by any cause within 90 days after the esophagectomy.

Length of hospital stay: The length of in-hospital stay was defined as the time in days from the esophagectomy to discharge.

3.3.6 Statistical analysis

Comparisons between the two groups were made using Student's t-test for means, and Fisher's exact test or Chi-square tests for binomial outcomes. Multivariable logistic regression was performed for anastomotic leakage leading to Clavien-Dindo score IVa or worse. Confounding variables that were used in the multi-variable model were age, sex, ASA score (193, 194), smoking status, clinical T-stage and N-stage, tumor location, surgical approach, Charlson Comorbidity Index (192, 195), and alcohol abuse. STATA/IC 13.1 software (StataCorp. LP, College Station, Texas, USA) was used for all statistical analyses.

3.3.7 Ethics

Approval was granted from the regional research ethics committee of Stockholm (reg. no. 2014/1093-31/1).

3.4 PAPER III

3.4.1 Study design

Analysis of the primary outcome; complete histological regression, and three year follow-up of overall survival and disease-free survival in the NeoRes trial was performed.

3.4.2 Definitions of outcomes

All surgical specimens were reviewed by an expert pathologist at the Karolinska University Hospital in Stockholm, who was blinded to the randomization outcome of each individual patient.

The tumor regression grade was defined according to Chirieac (124) as the quota of tumor cells and fibrosis and was assessed on a four-grade scale. TRG 1 represents histological complete response; TRG 2 represents 1–10% remaining tumor cells; TRG 3, 11–50% tumor cells; and TRG 4, > 50% tumor cells. Case-record forms and patient files were reviewed, particularly with regard to evidence of disease progression or of recurrence, and in the case of death during the first three years of follow-up; the cause of death was also carefully assessed.

Survival was calculated from the day of inclusion until death of any cause during the first three years.

3.4.3 Statistical analysis

Data were primarily analysed according to the intention-to-treat principle in all randomized patients. Per protocol was also performed where the patients were defined as those who had received three cycles of neoadjuvant chemotherapy and, in the nCRT group; 40 Gy radiotherapy, in accordance with the study protocol. Comparisons between the groups were done with the Chi-square test and Fisher's exact test. The Cox proportional hazard model and the log rank test were used. The significance level was set at 5%. Subgroup analyses by sex, age, ECOG performance score, histological tumor type, tumor location, clinical T-stage, and N-stage were prespecified. STATA/IC 13.1 software (StataCorp. LP, College Station, Texas, USA) was used for all statistical analyses.

3.5 PAPER IV

3.5.1 Study design

A cohort study population was collected between 1st January 2006 and 31st March 2014 using the prospectively registered exposure and outcome data retrieved from nationwide, population-based registers crossed-matched by personal registration (social security) numbers assigned to all Swedish residents. All patients who underwent esophagectomy with curative intent due to cancer in the esophagus or GEJ including Siewert types I and II were included in the study. Inclusion tumor stage was T1-T4 with any N stage, with the exception of T1N0. Potential confounding baseline variables including tumor characteristics, age, sex, ASA score and Karnofsky performance score, were compiled. Postoperative morbidity was reported in the registry as surgical or non-surgical complications.

3.5.2 The Swedish National Register for Esophageal and Gastric Cancer (NREV)

The register was started in 2006, and since then more than 95% of all patients with esophageal or gastric cancers diagnosed in Sweden have been registered. A validation study has shown the accuracy of the data in the registry to be 94% (196). Data are reported to the central register in an online data form by the physician who is responsible for treating the patients at each individual time point. The first form is reported at the time of the diagnosis, the second at surgery, the third at the first postoperative follow-up, and the fourth at one year after diagnosis or upon death. Data are monitored by the six Regional Cancer Centers and regular follow-ups are performed in order to complete the register. Death dates were retrieved from the Swedish population register (197).

3.5.3 Exposure

The neoadjuvant chemotherapy regimens in Sweden are specified in guidelines written by the regional cancer centers. During the study period, patients with adenocarcinomas received either three cycles of cisplatin 100 mg/m^2 d and 5-fluorouracil 750 mg/m^2/24 hours, or perioperative administration of epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and fluorouracil 200 mg/m^2/24 hours, according to the MAGIC regimen (103). Squamous cell carcinomas were treated with three cycles of cisplatin 100 mg/m^2 d and 5-fluorouracil 750 mg/m^2/24 hours. The standard neoadjuvant radiotherapy was delivered in 2 Gy fractions for a total dose of 40 Gy (198). Patients were divided into three groups according to registered preoperative treatment strategy: SA, nCT, and nCRT.

3.5.4 Definitions of outcomes

All reported complications were included in the analysis. The Clavien-Dindo score for severity grade of complications was included in the register from January 2012 onwards, but contained too few patients to allow for a meaningful analysis. Postoperative complications were divided into surgical and non-surgical complications. The definitions of outcomes used in the register were applied in the study:

Surgical complications included anastomotic leakage (defined as assessed with CT scan with an oral water-soluble contrast medium, and any uncertainty was followed up with endoscopy), conduit necrosis, bleeding, chylothorax, or recurrent laryngeal nerve paralysis.
Bleeding was defined as a blood loss of more than 2 litres or requiring surgical re-intervention.
Conduit necrosis was defined as clinically significant ischemia with perforation or ulcer.
Abdominal or thoracic abscess was reported when radiologically or surgically verified with a size of at least 3x3 cm.
Significant lymph leakage was defined when drainage was required for more than 7 days or surgical re-intervention was needed.
Recurrent laryngeal nerve paralysis was diagnosed by an otolaryngologist.
Non-surgical complications included cardiovascular complications, respiratory failure, pneumonia, and infections not related to the operation field.
Pneumonia was defined by chest x-ray findings and fever, cough and/or dyspnoea.
Septicemia was defined as body temperature above 38.3 C (101 F) or below 36 C (96.8 F), and a positive blood culture.
Cardiovascular complications included cardiac arrhythmias requiring medical treatment, myocardial infarction, and cerebral embolism.
Pulmonary embolism was defined as radiologically confirmed emboli requiring treatment.
Survival was calculated from the date of the diagnosis until death or censoring on 9th April 2014.

3.5.5 Statistical analysis

The associations between neoadjuvant treatment and postoperative complications, mortality and long-term survival were investigated. Multivariable logistic regression modelling, the Chi-square test and Fischer´s exact test were used for binomial outcomes. The Cox proportional hazard model was used for the survival analyses. A multivariable model tested various potential confounding variables: age, sex, ASA score I-IV (199), Karnofsky performance score (195) (0-100), cT stage, cN stage (186), histological tumor type, tumor location, year of treatment, and centre. The final model was designed through a stepwise simple testing of all relevant potential confounding factors. A propensity score was calculated using clinical T- and N-stage, tumor location, tumor type, sex, age, ASA-score, performance score. Regression analysis with covariate adjustment using the propensity score were performed and did not significantly differ from the Cox regression (data not shown). Analyses were performed using STATA® version 13 software (StataCorp LP, College Station, Texas, USA).

3.5.6 Ethics

Approval was granted by the Regional Research Ethics Committee of Stockholm (registration nr: epn 2013/596-31/3).

4 RESULTS

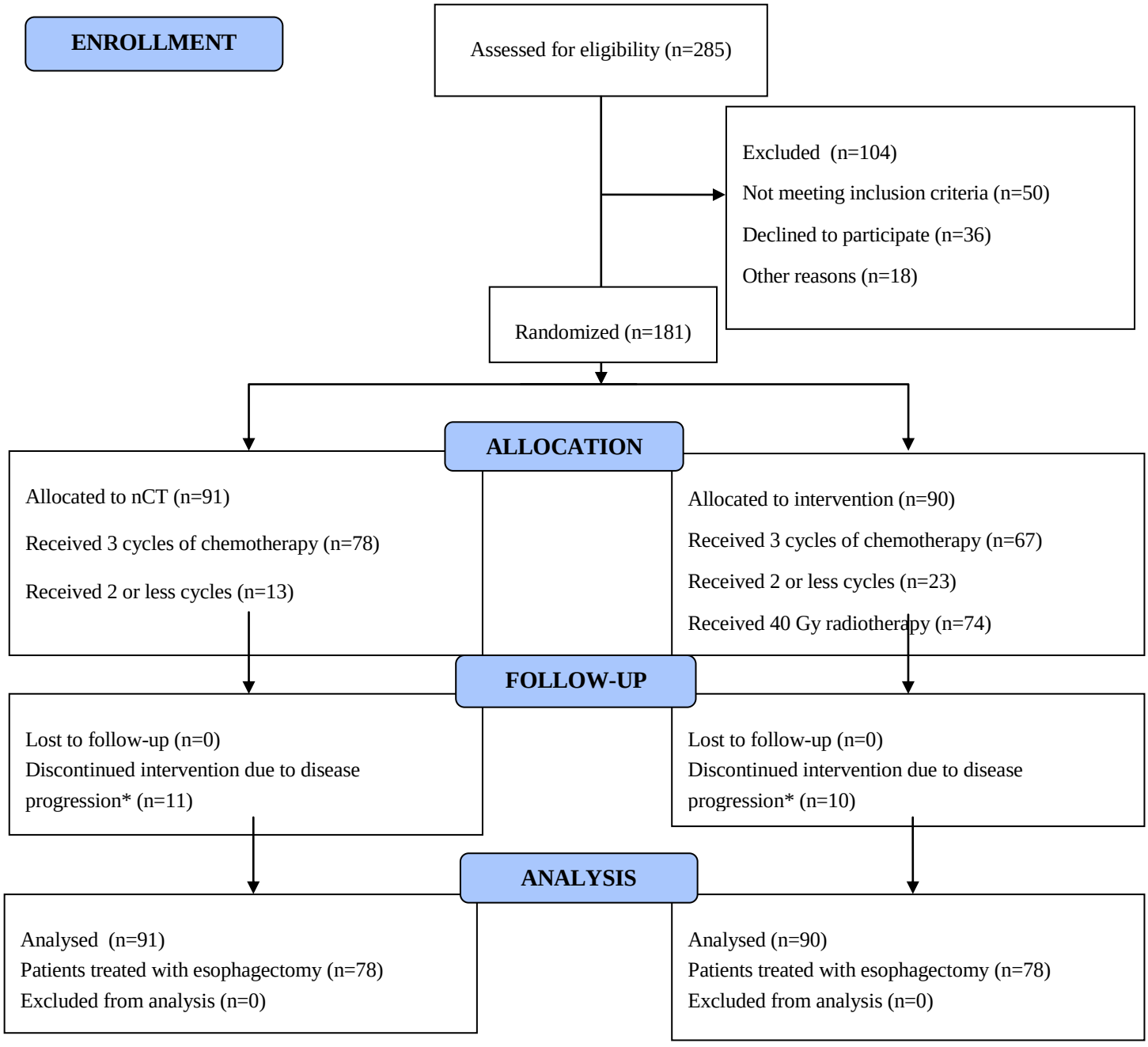
4.1 PAPER I

4.1.1 Study enrolment and neoadjuvant treatment

During the study period, 285 patients were screened for inclusion. Of these, 181 patients were randomized, 91 to nCT and 90 to nCRT (Figure 4). The median observation time after randomization was 57 months. Randomization resulted in a well-balanced distribution of baseline characteristics (Table 4). Seventy-four patients in the nCRT study arm (82%) received the planned 40 Gy radiotherapy dose, among those that did not receive the full radiotherapy the median dose was 27 Gy. In the nCT study arm 78 patients (85%) received three cycles, while the corresponding number of patients in the nCRT arm was 67 (74%, p=0.06). In total, 98 severe adverse events (SAE) were registered, and of these, 41 (42%) occurred in the nCT group and 57 (58%) in the nCRT group (p=0.14). Three of these events were lethal. One patient died from neutropenia and septicaemia in the nCT arm, whereas two patients died in the nCRT arm: one from pulmonary embolism and the other from tumor occlusion of the trachea (Table 5).

The median time between randomization and surgery was 92 days in the nCT arm and 97 days in the nCRT arm. Of the 181 randomized patients, 160 (88%) came to surgery, and 156 (86%) underwent esophagectomy. Subgroup analysis stratifying for tumor type showed a statistically significant difference in the resection rate for patients with SCC; 19 (76%) in the nCT group and 24 (96%) in the nCRT group (p=0.04). The corresponding figures for AC were 59 patients (89%) in the nCT group and 54 (83%) in the nCRT group (p=0.29).

Figure 4. *Study enrollment in the NeoRes trial.*



******* *The reasons for not being surgically explored were (i) SAEs (three in each treatment group), (ii) disease progression (six after nCT and three after nCRT), and (iii) general physical deterioration with or without the registration of SAEs (one patient after nCT and five after nCRT). Two patients in each treatment arm were found to have metastatic disease at surgery, and consequently resection was aborted.*

***Table 4**. Characteristics of patients with cancer in the esophagus and gastro-esophageal junction according to allocated treatment.*

	(%)	nCT	nCRT
Age			
Median (range)		63 (37–75)	63 (38–74)
Gender			
Female		14 (15)	18 (20)
Male		77 (85)	72 (80)
Tumor type			
Adenocarcinoma		66 (73)	65 (72)
Squamous-cell carcinoma		25 (27)	25 (28)
Tumor location[a]			
Proximal		2 (2)	2 (2)
Middle		13 (14)	13 (14)
Distal		59 (65)	61 (68)
Gastro-esophageal junction		17 (19)	14 (16)
Clinical T-stage[b]			
T1		1 (1)	1 (1)
T2		31 (34)	31 (34)
T3		59 (65)	58 (64)
Clinical N-stage[b]			
N0		34 (37)	33 (37)
N-positive		57 (63)	57 (63)
ECOG performances status[c]			
ECOG 0		77 (85)	75 (83)
ECOG 1		14 (15)	15 (17)
Preoperative endoscopic ultrasound		63 (69)	65 (72)
Preoperative FDG-PET		41 (45)	46 (51)
Surgical approach			
Ivor Lewis esophagectomy		54 (69)	49 (63)
Transhiatal esophagectomy		7 (9)	8 (10)
Three-stage esophagectomy		16 (21)	19 (24)
Total gastrectomy		1 (1)	2 (2)
No resection		13 (14)	12 (13)
Total		91 (50)	90 (50)

***a)** Tumor location was assessed by endoscopy and computed tomography. **b)** Tumor stage (TNM) was assessed by endoscopy and computed tomography with optional use of endoscopic ultrasonography (EUS) and PET-CT. **c)** ECOG performance status score 0–5.*

Table 5. *Chemotherapy according to protocol, severe adverse events during neoadjuvant treatment and postoperative results according to randomization.*

	(%)	nCT	nCRT	*p-value*
40 Gy neoadjuvant radiotherapy		-	74 (85)	-
3 cycles of neoadjuvant chemotherapy		78 (86)	67 (74)	*0.06*
Severe adverse events:				
Infection		5	5	
Nausea and vomiting		2	6	
Nutritional deficiency		13	13	
Gastrointestinal symptoms		1	5	
Cardiovascular event		7	14	
Renal failure		7	4	
Infection		5	5	
Neutropenia/thrombocytopenia		2	5	
Other		3	3	
Death*		1	2	
Total number SAE		41	57	*0.14*

** In the nCRT group one patient died from pulmonary embolism and from occlusion of the trachea; in the nCT group one patient died due to neutropenia and septicaemia.*

4.1.2 Postoperative outcome

There was no postoperative 30-day mortality in either group. Six (8%) patients in the nCRT group and two (3%) in the nCT group died within 90 days of surgery. The difference was not statistically significant (p=0.28). Of the two deaths after nCT one patient died because of postoperative respiratory failure, without any surgical complication, while the other died due to rapid tumor progression, without any serious postoperative complication. All five patients who died within 90 days after nCRT did so due to serious complications, although two also had signs of early tumor recurrence. Three of these patients had surgical complications, of which one had gastric conduit necrosis and two died in progressive respiratory failure (Table 6).

The total surgical complication rate was 38% (n = 29) in the nCRT group and 35% (n = 27) in the nCT group. The corresponding figures for nonsurgical complications were 31% (n = 24) and 21% (n = 16). The proportion of patients suffering from any type of complication was 55% (n = 42) for nCRT and 45% (n = 35) for nCT (p=0.23). Data regarding individual and pooled complication types are shown in Table 6.

Logistic regression analysis of surgical and non-surgical complications, as well as for severe complications (Clavien-Dindo IIIb or higher), with adjustment for age, gender, T-stage, tumor location and WHO classification grade, did not significantly differ from the univariate results, thus indicating a low risk of confounding owing to failure in randomization (data not shown).

Thirty percent (n = 23) of the patients resected after nCRT experienced a complication that scored IIIb or higher in the Clavien-Dindo system, corresponding to reintervention in general

anesthesia, admission to intensive care for single or multiple organ failure, or death due to complication. The corresponding figure was 17% (n = 13) among patients operated on after nCT (p=0.05). The mean CCI was 41 in the nCRT group and 31 in the nCT group (p=0.03). The median Clavien-Dindo complication severity score among those with any complication was IIIb in the nCRT group (n = 42) and IIIa in the nCT group (n = 35). This difference was statistically significant (p=0.001).

***Table 6**. Postoperative complications, mortality and Clavien-Dindo score.*

	(%) nCRT	nCT	p-value
30-day mortality	1 (1)	0 (0)	1.0
90-day mortality	6 (8)	2 (3)	0.28
Surgical complication[a]	29 (38)	27 (35)	0.69
Non-surgical complication[b]	24 (31)	16 (21)	0.13
Any complication[c]	42 (55)	35 (45)	0.23
Anastomotic leakage[d]	10 (13)	7 (9)	0.45
Respiratory complication[e]	17 (22)	10 (13)	0.14
Cardiovascular complication[f]	7 (9)	4 (5)	0.37
Clavien-Dindo score[g]			
I	1 (1)	3 (4)	
II	9 (12)	7 (9)	
IIIa	9 (12)	12 (15)	
IIIb	14 (18)	8 (10)	
Iva	4 (5)	4 (5)	
Ivb	0 (0)	0 (0)	
V	5 (6)	1 (1)	
Total:	42 (55)	35 (45)	
Clavien-Dindo score IIIb or higher	23 (30)	13 (17)	0.05
Median Clavien-Dindo score	IIIb	IIIa	0.001
Mean CCI	41	31	0.03

***a)** Surgical complications—for example, anastomotic leakage, conduit necrosis, bleeding, chylothorax, and recurrent laryngeal nerve paralysis. **b)** Nonsurgical complications—for example, cardiovascular complications including arrhythmias requiring treatment and thromboembolism, respiratory failure, and infections not related to the operation field. **c)** Patients suffering from either surgical or nonsurgical complications. **d)** Anastomotic leakage was assessed using CT scan with an oral water-soluble contrast medium, and any uncertainty was followed up with endoscopy. **e)** Respiratory complications include pneumonia, pleural effusion requiring postoperative placement of drains, and respiratory failure in general. **f)** Cardiovascular complications include cardiac arrhythmias requiring treatment, myocardial infarction, cerebral embolism, and pulmonary embolism. **g)** The severity of complications scored according to the Clavien-Dindo system and the Comprehensive Complication Index.*

4.2 PAPER II

4.2.1 Study sample and treatment

Seventy consecutive patients who, due to cancer, underwent esophagectomy with cervical esophagogastrostomy were included in this analysis. The non-irradiated group (non-RT) consisted of 42 patients, 10 of whom received neoadjuvant chemotherapy without radiation, and 32 treated with esophagectomy alone. The irradiated, nCRT group, comprised 28 patients. The Charlson comorbidity score was higher in the non-RT group but the difference was not statistically significant; ASA classification was similar in both groups. The mean age was higher in the non-RT group compared to the nCRT group, at 68 vs. 63 years (Table 7).

The standard radiotherapy dose of 40 Gy was given to 25 patients, while two received 38 Gy, and one 50 Gy. The radiation dose plan assessment was performed on 22 of the 28 patients in the nCRT group. We were unable to retrieve dose planning data in six cases either due to software updates or because patients had received their radiotherapy at other hospitals. The analyses showed that 20 out of 22 patients (93%) were planned to be irradiated at the site of the future anastomosis in the gastric fundus. Between 15 - 100% of the full dose was planned to be delivered to the gastric fundus. The mean dose was 17.3 Gy, and the median dose was 10.6 Gy (Figure 5). An example of a dose plan CT image is shown in Figure 6.

4.2.2 Anastomotic complications

In total there were 28 anastomotic complications in the 70 patients (40%): in 16 of the 42 non-RT patients (38%) and in 12 of the 28 nCRT patients (43%, p=0.69). Among the patients in the non-RT group who received neoadjuvant chemotherapy, there were 3 (30%) cases of anastomotic complications.

Among the patients in the nCRT group, the anastomotic complications were classified as Clavien-Dindo grade IVa or higher, indicating a complication demanding ICU care for single organ failure or worse, in 11 of 28 patients (39%) compared to in 7 of 42 (17%) in the non-RT group (p=0.03). In the nCRT group, 3 patients (11%) died due to anastomotic complications compared to none in the non-RT group (p=0.06, Table 8 and Figure 7). The crude odds ratio for a Clavien-Dindo grade IVa or worse in the nCRT group was 3.2 (95% CI: 1.1-9.8, p=0.038), and adjusted for the Charlson Comorbidity Index and T-stage, the odds ratio increased to 6.0 (95% CI: 1.52 -23.50, p=0.021) when compared to the non-RT group.

Table 7. *Patient characteristics, tumor data and surgical approaches.*

(%)	Non-RT	nCRT	p-value
Surgery alone	32 (76)	0 (0)	
Neoadjuvant chemotherapy nCT	10 (24)	0 (0)	
Neoadjuvant chemoradiotherapy nCRT	0 (0)	28 (100)	
Female	15 (36)	4 (14)	0.048
Male	27 (64)	24 (86)	
Age (SD)	71 (11.6)	64 (9.5)	0.016
Smoking	28 (67)	24 (86)	0.10
Alcohol abuse[a]	7 (17)	5 (18)	0.90
WHO performance status[b]			0.46
WHO 0	36 (86)	26 (93)	-
WHO 1	6 (14)	2 (7)	-
ASA score			<0.001
I	18 (43)	16 (57)	
II	15 (36)	8 (29)	
III	9 (21)	4 (14)	
Charlson Comorbidity Index[c]			0.34
0	23 (55)	19 (68)	
1	11 (26)	7 (25)	
2	8 (19)	2 (7)	
Adenocarcinoma	22 (52)	17 (61)	0.71
Squamous cell carcinoma	17 (40)	10 (36)	
Other	3 (7)	1 (4)	
Tumor location[d]**:**			0.78
Proximal	1 (2)	2 (7)	
Middle	11 (26)	7 (25)	
Distal	19 (45)	11 (39)	
GEJ	11 (26)	8 (29)	
T-stage[e]**:**			0.06
I	9 (21)	0 (0)	
II	8 (19)	5 (18)	
III	22 (53)	21 (75)	
IV	3 (7)	2 (7)	
N-stage[f]**:**			0.39
N0	23 (55)	12 (55)	
N1	12 (29)	9 (41)	
N2	2 (5)	1 (5)	
Missing	5 (12)	0 (0)	
Surgical approach[g]**:**			0.031
Transhiatal esophagectomy	17 (40)	3 (11)	
Minimally invasive esophagectomy	12 (29)	12 (43)	
Three-field esophagectomy	10 (24)	7 (25)	
Thoracoscopic hybrid esophagectomy	3 (7)	6 (21)	

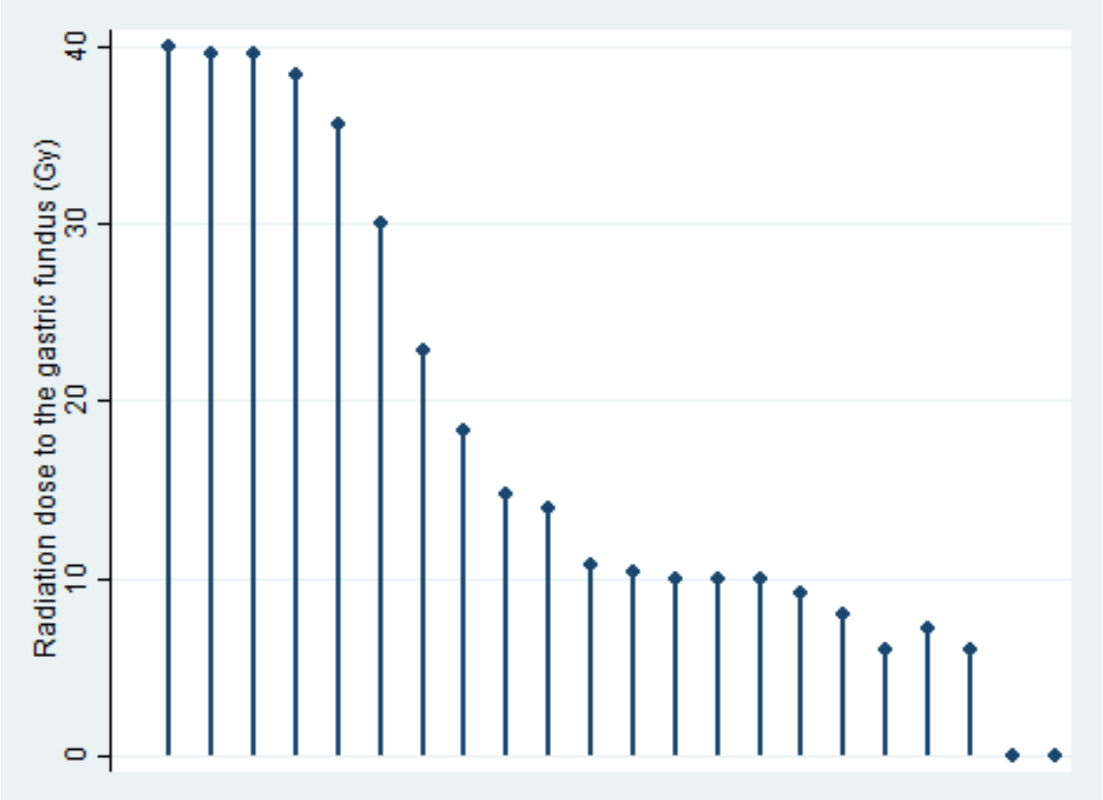
a) *Alcohol abuse was defined as an overconsumption leading to clear clinical consequences* ***b)*** *WHO performance status score 0–5.* ***c)*** *Charlson comorbidity index at baseline.(192).* ***d)*** *Tumor location by endoscopy and computed tomography.* ***e)*** *T stage by endoscopy and CT with optional use of endoscopic ultrasonography (EUS) and PET-CT.* ***f)*** *Clinical n stage by endoscopic ultrasound or FDG-PET-CT.* ***g)*** *All procedures included a cervical anastomosis.*

Table 8. *Postoperative outcome.*

(%)	non-RT	nCRT	p-value
30-day mortality	0 (0)	2 (7)	0.08
90-day mortality	3 (7)	4 (14)	0.33
Length of stay, median days	25	19	0.41
Surgical complication[a]	25 (60)	14 (50)	0.43
Non-surgical complication[b]	37 (88)	23 (82)	0.49
Any complication[c]	39 (93)	23 (82)	0.25
Pneumonia	18 (43)	16 (57)	0.24
Respiratory insufficiency	16 (38)	14 (50)	0.32
Cardiovascular complication[d]	14 (33)	4 (14)	0.10
Postoperative ICU care, median days	11	17	0.42
Esophageal stricture	20 (48)	8 (29)	0.29
Anastomotic complication[e]	16 (38)	12 (43)	0.69
Clavien-Dindo score for anastomotic complication[f]			
I	0 (0)	0 (0)	-
II	1 (2)	0 (0)	-
IIIa	2 (5)	1 (4)	-
IIIb	6 (14)	0 (0)	-
IVa	5 (12)	4 (14)	-
IVb	2 (5)	4 (14)	-
V	0 (0)	3 (11)	-
Total:	16 (38)	12 (43)	-
Median Clavien-Dindo score	IIIb	IVb	0.002

a) *Surgical complications—for example, anastomotic leakage, conduit necrosis, bleeding, chylothorax, and recurrent laryngeal nerve paralysis.* ***b)*** *Nonsurgical complications—for example, cardiovascular complications including arrhythmias requiring treatment and thromboembolism, respiratory failure, and infections not related to the operation field.* ***c)*** *Patients suffering from either surgical or nonsurgical complications.* ***d)*** *Cardiovascular complications include cardiac arrhythmias requiring treatment, myocardial infarction, cerebral embolism, and pulmonary embolism.* ***e)*** *Anastomotic complication was assessed using CT scan with an oral water-soluble contrast medium, and any uncertainty was followed up with endoscopy.* ***f)*** *The severity of complications was scored according to the Clavien-Dindo system for classifying surgical complications.*

Figure 5. *Radiation exposures at the planned site of anastomosis in the nCRT group***.**

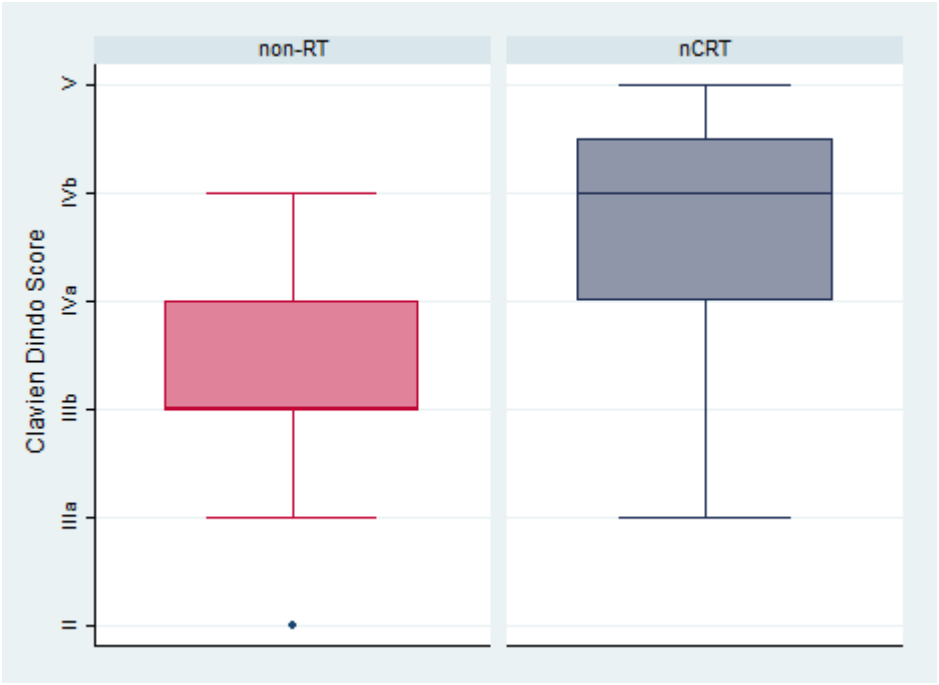


The estimated dose to the site of the future gastroesophageal anastomosis in the 22 analyzed patients. Mean dose was 17.3 Gy (95% CI 11.3 - 23.3), and median dose was 10.6 Gy.

Figure 6. *Computerized tomography image showing radiation dose planning.*

Primary tumor in the gastroesophageal junction and targeted lymph nodes delineated with red lines. Full dose of 40 Gy area in light red color, surrounding partially irradiated area in yellow, green and blue. The future site of anastomosis in the gastric fundus is within the partial radiation target area.

Figure 7. *Distribution of Clavien-Dindo grade after anastomotic complication.*



Box plots of the distribution of Clavien-Dindo scores after anastomotic complications in the two groups. The median score was IIIb in the non-RT group, and IVb in the nCRT group (p=0.002).

4.3 PAPER III

4.3.1 Pathological evaluation and 3-year survival

Histological complete response was achieved in 7 (9%) of the patients in the nCT arm, versus 22 (28%) in the nCRT arm (p=0.002). Of the patients with histological complete response, 26 (90%) did not have any metastatic lymph nodes, while three patients (10%), all treated with nCRT, had at least one metastatic lymph node. A median of 22 lymph nodes was found in patient specimens after nCT, compared to 16 after nCRT (p=0.003). Of patients resected in the nCT arm, 48 (62%) had lymph-node metastases, versus 27 (35%) in the nCRT arm (p=0.001). R0 resection was achieved in 58 (74%) patients in the nCT arm, versus 68 (87%) in the nCRT arm (p=0.04, Table 9).

Three-year overall survival rate using intention-to-treat analysis was 49% in the nCT arm, and 47% in the nCRT arm (p=0.77). The crude hazard ratio (HR) for death during the first three years after randomization was, in the nCRT arm, 1.09 (95% CI 0.73–1.64), compared to the nCT arm, and the corresponding HR adjusted for sex, age, ECOG performance status, histological type, clinical T-stage, and N-stage was 1.11 (95% CI 0.74–1.67). The crude HR for patients with AC in the nCRT arm was 1.22 (95% CI 0.76–1.94), and the adjusted HR was 1.11 (95% CI 0.74–1.67). For patients with SCC in the nCRT arm, the crude HR was 0.83 (95% CI 0.37–1.89), and the adjusted HR was 0.52 (0.20–1.36). Per protocol analyses of overall survival stratified by histological tumor type indicated similar numbers with lower survival in patients with AC after nCRT and slightly improved survival for patients with SCC after nCRT. These differences did not reach statistical significance. Patients who responded to the neoadjuvant treatment with TRG 1 or 2 had a three-year survival rate of 74%, compared with 46% for TRG 3 or 4 (p=0.001), HR =0.40 (95% CI 0.23–0.73, Figure 8).

The progression-free three-year survival rate was 44% in both treatment arms. Among patients with AC, 41% exhibited progression-free three-year survival in the nCT arm, and 40% in the nCRT arm did the same. The corresponding figures for the patients with SCC were 52% in the nCT arm and 56% in the nCRT arm (Figure 9). For data on incidence of local and distant recurrence see Table 9.

Analysis of the causes of death by follow-up year revealed significantly more deaths in the first year after randomisation related to causes other than tumor recurrence; these were, in effect, SAEs during neoadjuvant therapy and postoperative complications: in the nCRT arm, 11 of 24 patients (46%) experienced such events, and in the nCT arm, 3 of 20 (15%) did (p=0.04, Figure 10).

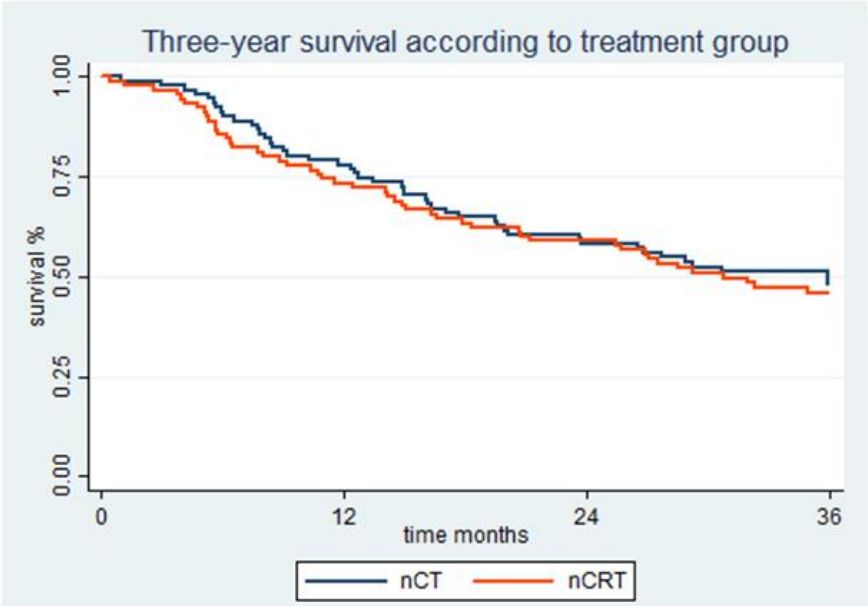
Table 9. *Outcome of treatment according to allocated neoadjuvant therapy and subgroup analysis of adenocarcinoma and squamous-cell carcinoma.*

	(%)	nCT	nCRT	p-value
Tumor regression grade[a]*				<0.001
1: Histological complete response		7 (9)	22 (28)	0.002
2: 1–10% tumor cells		5 (6)	19 (24)	
3: 11–50% tumor cells		5 (6)	14 (18)	
4: >50% tumor cells		61 (78)	23 (29)	
Surgical resection**		78 (86)	78 (87)	0.85
R0 resection[c]*		58 (74)	68 (87)	0.04
Tumor-free longitudinal margin*		75 (96)	77 (99)	0.31
Tumor-free circumferential margin*		60 (78)	69 (88)	0.09
Lymph-node metastasis*		48 (62)	27 (35)	0.001
Three-year overall survival**		45 (49)	42 (47)	0.77
Progression-free 3-year survival[b]**		40 (44)	40 (44)	0.95
Length of hospital stay (median days)		16	19	0.29
Recurrent disease*		35 (45)	28 (36)	0.25
Local recurrence*		15 (19)	13 (16)	0.68
Outcome of treatment in patients with AC				
Tumor regression grade[a]*				<0.001
1: Histological complete response		4 (7)	12 (22)	
2: 1–10% tumor cells		3 (5)	15 (28)	
3: 11–50% tumor cells		4 (6)	10 (19)	
4: >50% tumor cells		48 (81)	17 (31)	
Surgical resection**		59 (89)	54 (83)	0.29
R0 resection[c]*		58 (74)	68 (87)	0.04
Lymph-node metastasis*		38 (64)	21 (39)	0.007
Recurrent disease*		31 (53)	20 (37)	0.10
Local recurrence*		13 (22)	9 (16)	0.44
Three-year survival**		32 (48)	28 (43)	0.54
Progression-free three-year survival[b]**		27 (41)	26 (40)	0.92

Outcome of treatment in patients with SCC			
Tumor regression grade[a]*			0.04
1: Histological complete response	3 (16)	10 (42)	
2: 1–10% tumor cells	2 (11)	4 (17)	
3: 11–50% tumor cells	1 (5)	4 (17)	
4: >50% tumor cells	13 (68)	6 (25)	
Surgical resection**	19 (76)	24 (96)	0.04
R0 resection[c]*	16 (84)	20 (83)	0.94
Lymph-node metastasis*	10 (53)	6 (25)	0.06
Recurrent disease*	4 (21)	8 (33)	0.37
Local recurrence*	2 (10)	4 (17)	0.52
Three-year survival**	13 (52)	14 (56)	0.78
Progression-free three-year survival[a]**	13 (52)	14 (56)	0.78

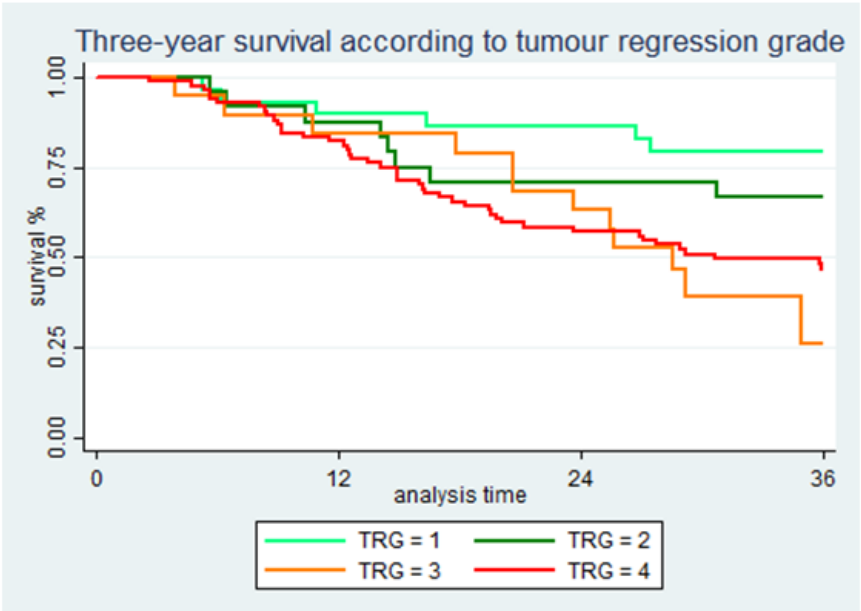
= percent of resected patients, ** = percent of total,* ***a)* *The TRG was defined as the quota of tumor cells and fibrosis and was assessed on a four-grade scale. TRG 1: no tumor cells; TRG 2: 1–10% tumor cells; TRG 3: 11–50% tumor cells: and TRG 4: >50% tumor cells (11).* ***b)*** *Progression was defined as local or distant recurrence, death from any cause, and disseminated disease before or at surgery.* ***c)*** *The resection was considered R0 if there were no tumor cells within 1 mm of any resection margin.*

Figure 8. *Kaplan-Meier plots of overall three-year survival according to treatment group, tumor regression grade, tumor type, and per protocol analysis.*



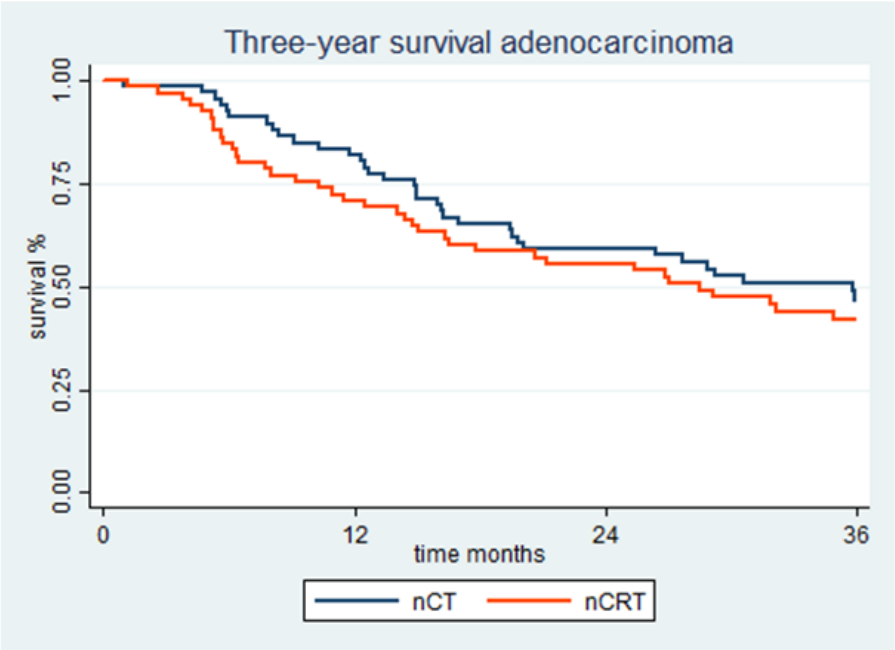
	Numbers at risk			
Follow up (months)	0	12	24	36
nCT	91	71	53	45
nCRT	90	66	53	42

a) *Estimated three-year survival of 181 patients with esophageal and gastro-esophageal junctional cancer, randomized to neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery. Intention-to-treat analysis: crude hazard ratio for death in the nCRT group was 1.09 (0.73–1.64), HR adjusted for sex, age, ECOG performance status, histological type, clinical T-stage, and N-stage: 1.11 (0.74–1.67).*



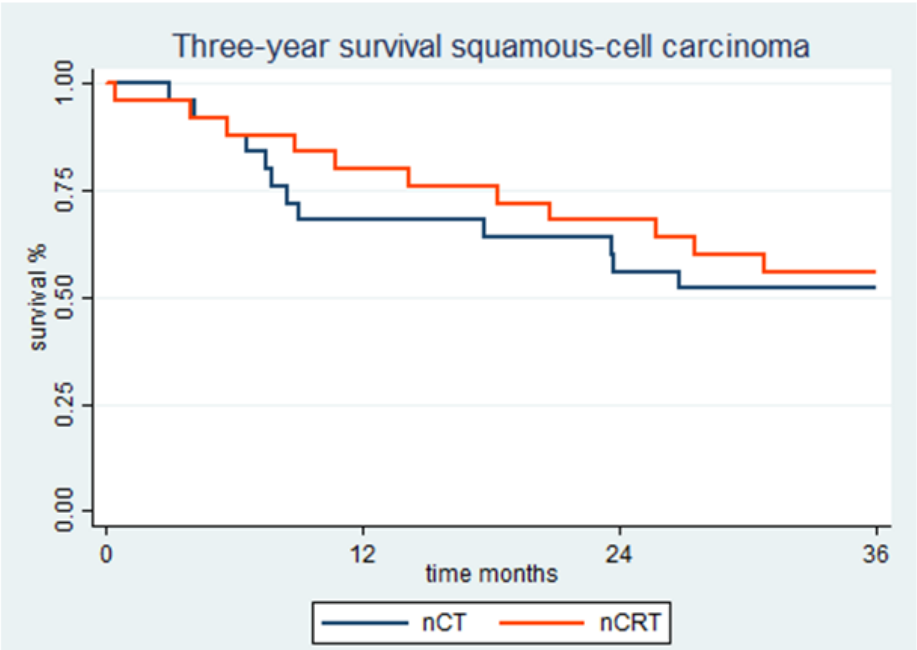
	TRG	Numbers at risk			
Follow up (months)		0	12	24	36
	1	28	25	24	22
	2	24	21	17	16
	3	19	16	12	7
	4	85	70	49	41

b) *Kaplan-Meier plot showing the estimated survival according to response to the neoadjuvant therapy (11). Patients with TRG 1 or 2 have a three-year survival rate of 74%, versus 46% for the patients with TRG 3 or 4 (p=0.001), HR =0.40 (95% CI 0.23–0.73).*



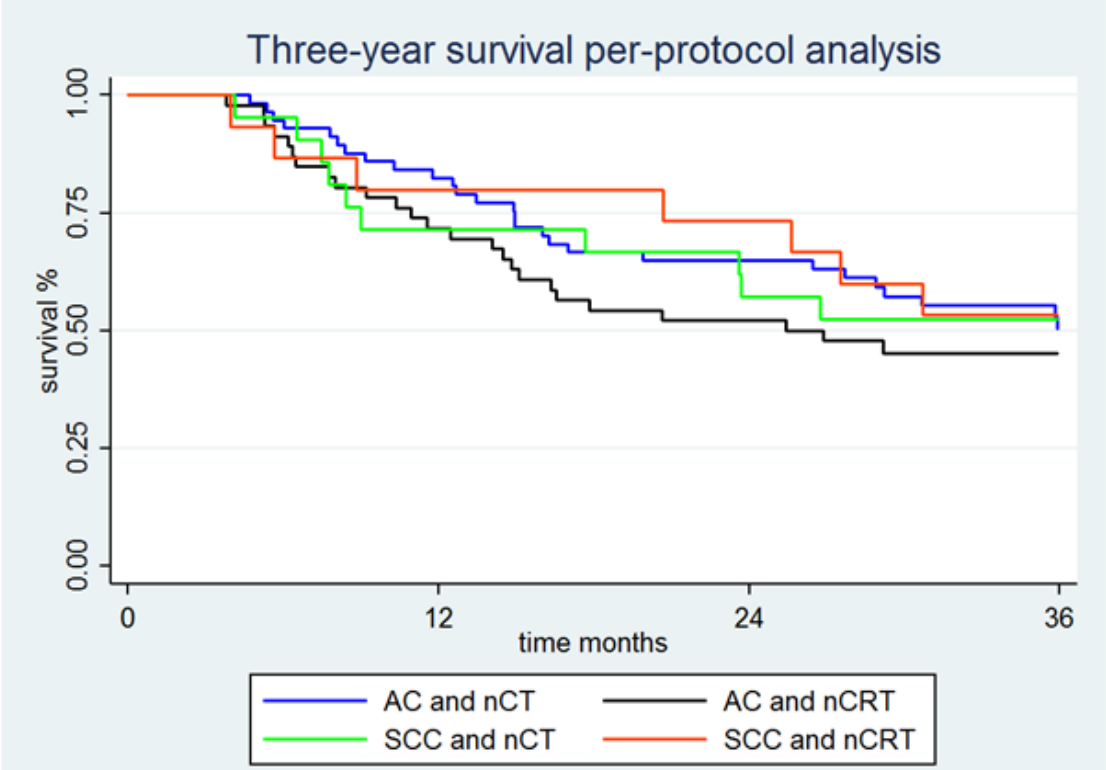
	Numbers at risk			
Follow up (months)	0	12	24	36
nCT	66	54	39	32
nCRT	65	46	36	28

c) *The crude hazard ratio in intention-to-treat analysis for patients with AC and nCRT was 1.22 (0.76–1.94), adjusted for sex, age, ECOG performance status, histological type, clinical T-stage, and N-stage: 1.20 (0.75–1.92).*



	Numbers at risk			
Follow up (months)	0	12	24	36
SCC and nCT	25	17	14	13
SCC and nCRT	25	20	17	14

d) *Patients with SCC and nCRT had in an intention-to-treat analysis HR =0.83 (0.37–1.89), adjusted for sex, age, ECOG performance status, histological type, clinical T-stage, and N-stage: 0.52 (0.20–1.36).*

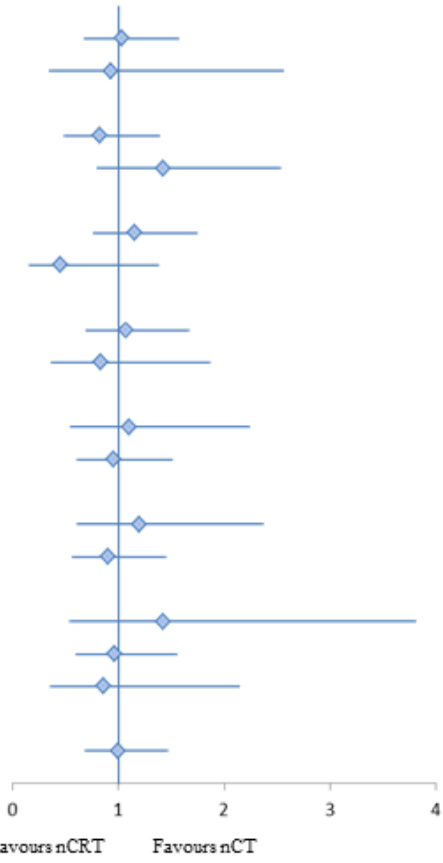


	Numbers at risk			
Follow up (months)	0	12	24	36
AC and nCT	57	47	37	24
AC and nCRT	50	36	27	18
SCC and nCT	21	15	12	9
SCC and nCRT	17	14	12	7

e) *Per protocol analyses of overall survival stratified by histological tumor type showing a trend for decreased survival for patients with AC after nCRT; crude HR 1.31 (95% CI 0.76–2.26) and a trend towards improved survival after nCRT for SCC patients: crude HR 0.90 (95% CI 0.34–2.38) compared to nCT.*

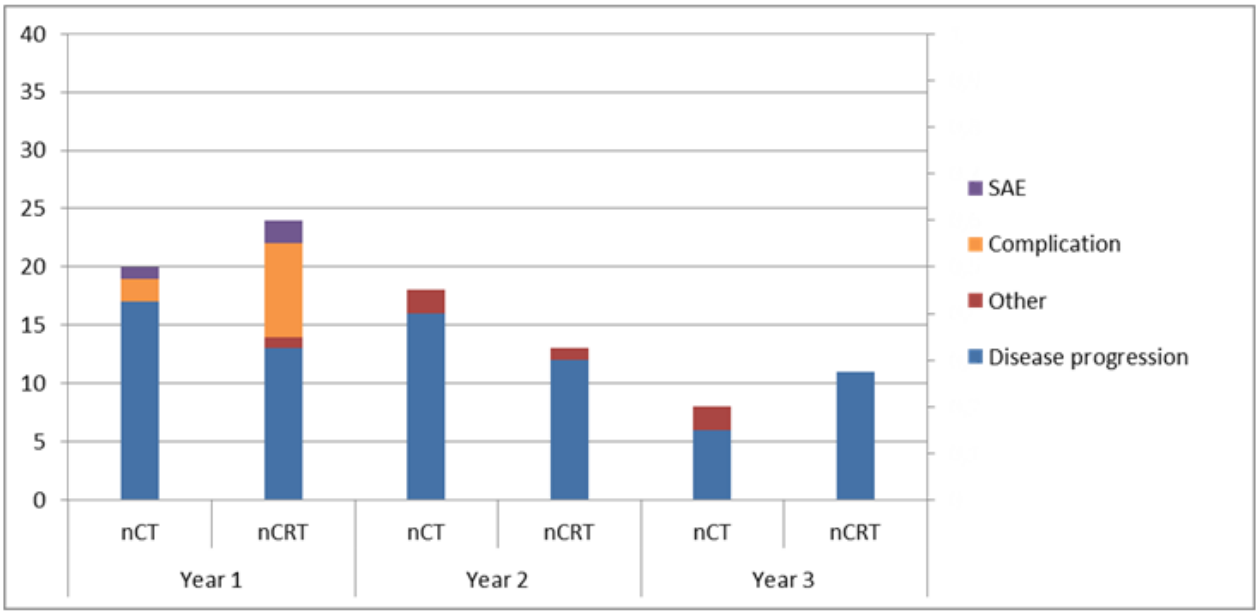
Figure 9. *Progression-free survival subgroup analysis.*

Subgroup	n	Number with event		Univariate HR (95% CI)	Multivariate HR (95% CI)
		nCT	nCRT		
Sex					
Men	149	44	42	1.03 (0.67-1.57)	1.0 (0.65-1.54)
Women	32	7	8	0.93 (0.34-2.56)	1.46 (0.49-4.32)
Age					
>60	115	29	26	0.82 (0.48-1.39)	0.79 (0.46-1.36)
<=60	66	22	24	1.42 (0.79-2.54)	1.44 (0.77-2.69)
WHO performance score					
0	152	43	45	1.15 (0.76-1.75)	1.07 (0.70-1.63)
1	29	8	5	0.45 (0.15-1.38)	2.40 (0.31-18.9)
Tumour type					
AC	131	39	39	1.07 (0.69-1.67)	1.06 (0.68-1.66)
SCC	50	12	11	0.83 (0.36-1.87)	0.53 (0.21-1.36)
Clinical T-stage					
T1/T2	64	15	15	1.10 (0.54-2.24)	0.95 (0.40-2.22)
T3	117	36	35	0.95 (0.60-1.51)	0.98 (0.61-1.60)
Clinical N-stage					
N0	67	16	17	1.20 (0.60-2.37)	1.48 (0.71-3.09)
N1	114	35	33	0.90 (0.56-1.46)	0.88 (0.54-1.42)
Location					
Proximal and middle	30	7	9	1.42 (0.53-3.81)	0.63 (0.15-2.69)
Distal	120	33	33	0.96 (0.59-1.56)	1.04 (0.63-1.72)
GOJ	31	11	8	0.86 (0.35-2.15)	0.96 (0.34-2.72)
All patients	181	51	50	1.0 (0.68-1.47)	1.02 (0.69-1.51)



Forest plot showing univariate hazard ratios for death or progression with 95% confidence intervals, according to baseline characteristics. Hazard ratios adjusted for baseline covariates are displayed under the multivariate HR caption.

Figure 10. *Causes of death during years 1–3 after randomization, according to treatment group.*



Analysis of the causes of death by follow-up year showed that during the first year after randomization, 11 of 24 (46%) in the nCRT arm and 3 of 20 (15%) in the nCT arm (p=0.04) died of causes other than tumor recurrence—that is, of severe adverse events during neoadjuvant therapy and postoperative complications.

4.4 PAPER IV

4.4.1 Study sample

In total, 1020 patients with esophageal or gastric cardia cancer type I and II underwent esophagectomy with curative intent, whereof neoadjuvant treatment was given to 521 (51%), and 499 (49%) were treated with SA. nCT was used for 205 (20%) patients and nCRT for 316 (31%). SA was more frequently practiced in the first years of the study period, while the use of nCT and nCRT increased over time. No patients were lost to follow-up and the median follow-up times were 5 years in the SA group, 3 years for nCT and 4 years in the nCRT group. Transthoracic open esophagectomy with the Ivor Lewis technique was the most commonly used surgical technique (Table 10). The overall 30- and 90-day mortalities were 1.7% and 5.4%, respectively. Anastomotic leakage occurred in 6.9% of the patients (Table 11). The overall five-year survival rate was 34.2% (Table 12).) The SA group had missing data concerning ASA-score in 10% and performance score in 13% of the cases, compared to 2-4% in the neoadjuvant treatment groups (Table 10).

4.4.2 Surgery alone vs. neoadjuvant chemotherapy

There were some differences between patients treated with SA and those who received nCT regarding baseline characteristics (Table 10). The patients in the SA group were older, had a lower average Karnofsky performance score and a higher ASA score. Tumor-specific characteristics also differed, with more advanced tumor stages and a higher frequency of

clinical N positive disease in the nCT group. The adjusted odds ratio for surgical complications in the nCT group was 2.71 (95% CI: 1.55-4.72) (Table 11). There was no difference between these groups concerning non-surgical complications, postoperative mortality, or R0 resection rates. The frequency of lymph node metastases was lower in those given nCT (p=0.013) (Table 12).

A Cox proportional hazards model showed a statistically significant improved overall survival for patients with squamous cell carcinomas after nCT, with adjusted HR: 0.39 (95% CI: 0.17-0.87) . For patients with adenocarcinoma, there was no significant difference in overall survival for the whole cohort, with adjusted HR: 0.93 (95% CI: 0.64-1.36), (Table 13, Figure 11). Stratified analysis, including only fit patients without comorbidity (Karnofsky performance status 100 and ASA score I), showed a strong trend for an advantage in overall survival after nCT, with an adjusted HR: 0.47 (95% CI: 0.21-1.04), compared to patients treated with SA (Table 13).

4.4.3 Surgery alone vs. neoadjuvant chemoradiotherapy

Baseline characteristics differed between the groups with older age, higher ASA score and lower Karnofsky performance score in the SA group. Histological tumor type and tumor locations were similar, but clinical T stage and clinical N stage were more advanced in the nCRT group (Table 10). The adjusted odds ratio for postoperative surgical complication in the nCRT group was 1.32 (95% CI: 0.84-2.10), suggesting a slightly increased risk, not reaching statistical significance however. The adjusted odds ratio for postoperative mortality within 90 days of surgery in the nCRT group was 2.37 (95% CI: 1.06-5.29) (Table 11). R0 resection rate was significantly higher after nCRT (P<0.001), and the risk for lymph node metastases was lower (P<0.001) (Table 12).

A trend towards improved overall survival after nCRT was observed in patients with squamous cell carcinomas, 54% 5-year survival compared to 30% after SA (p=0.066) adjusted HR: 0.74 (95% CI: 0.47-1.18) (Table 12, Table 13, Figure 8) and in stratified analysis including only fit patients without comorbidity hazard ratio point estimates dropped substantially with a significant survival advantage for nCRT compared to SA, adjusted HR 0.15 (95% CI: 0.04-0.59). There was no advantage in overall survival for patients with adenocarcinoma (Table 12, Table 13, and Figure 11).

4.4.4 Neoadjuvant chemotherapy vs. neoadjuvant chemoradiotherapy

The study groups were similar concerning age, gender and performance status. Proportions of histological tumor type differed between the treatment groups; 79 (25%) of the patients in the nCRT group were SCC, while only 19 (9%) of patients treated with nCT were SCC. Tumor location differed between groups as did clinical T stages, with more advanced stages in the nCRT group (p=0.001) (Table 10). In the nCRT group, 23 (7%) patients died within 90 days of surgery compared to 10 (5%) in the nCT group (p=0.27). Postoperative complications

were reported with similar frequency except those concerning septicaemia, which occurred in 5 (2%) patients after nCT and 20 (6%) patients after nCRT (p=0.04) (Table 11).

In patients with squamous cell carcinomas, there was no difference in number of identified lymph nodes or lymph node metastases between the nCT and nCRT groups. The R0 resection rate was significantly higher after nCRT (p=0.009). Pathological T stage was T2 in both groups, and the rates of histological complete response were similar (Table 12). There was no difference in long-term overall survival between the two groups (Table 13, Figure 11).

Concerning adenocarcinomas, the average number of lymph nodes found in the surgical specimen was 22 after nCT and 15 after nCRT (P<0.001). Lymph node metastases were found in 103 (61%) of the patients in the nCT group and in 83 (45%) of the patients in the nCRT group (p=0.003); the corresponding figures for R0 resection rates were 145 (86%) and 175 (95%), respectively (p=0.005). Median pathological tumor stage after nCT was T3. In the nCRT group the median pathological tumor stage was T2 (P<0.001). Histological complete response was achieved in 8 (4%) patients after nCT, and in significantly more, 40, patients after nCRT (17%, p<0.001) (Table 12). There was no statistically significant difference in survival between patients treated with nCT and nCRT (Table 13, and Figure 11).

Table 10. *Characteristics of patients with cancer in the esophagus or gastro-esophageal junction, by preoperative treatment.*

	SA	nCT	nCRT	SA /nCT	SA/ nCRT	nCT/ nCRT
n (%)					**p-value**	
Total	499 (49)	205 (20)	316 (31)	-	-	-
Median follow-up time (months)	63	38	49	<0.001	<0.001	0.004
Year of treatment (median)	2009	2011	2010			
Age, median (SD)	70 (9.8)	63 (7.9)	63 (10.0)	<0.001	<0.001	1.0
Gender				0.009	0.002	0.98
Female	123 (25)	32 (16)	49 (16)			
Male	376 (75)	173 (84)	267 (84)			
Performance status[a]				0.010	0.063	0.50
100	220 (51)	127 (63)	176 (58)			
80	182 (42)	69 (34)	117 (39)			
60	30 (7)	5 (2)	10 (3)			
40	1 (0)	0 (0)	0 (0)			
Missing data	66	4	13			
ASA score[b]				0.010	<0.001	0.058
I	124 (28)	69 (34)	131 (43)			
II	220 (49)	107 (53)	149 (49)			
III	99 (22)	26 (13)	24 (8)			
IV	6 (1)	0 (0)	0 (0)			
Missing data	50	3	12			
Histological tumor type				<0.001	0.24	<0.001
Adenocarcinoma	338 (68)	182 (89)	229 (73)			
Squamous cell carcinoma	136 (28)	19 (9)	79 (25)			
Other	20 (4)	4 (2)	7 (2)			
Tumor location[c]				0.002	0.36	0.001
Proximal	16 (3)	1 (0)	8 (3)			
Middle	71 (15)	12 (7)	44 (15)			
Distal	230 (50)	96 (53)	169 (56)			
GEJ	146 (32)	73 (40)	81 (27)			
Missing data	36	23	14			
Clinical T stage[d]				0.023	<0.001	0.001
T1	4 (1)	0 (0)	0 (0)			
T2	191 (48)	70 (41)	69 (24)			
T3	199 (50)	96 (56)	206 (72)			
T4	2 (1)	5 (3)	10 (4)			
Missing data	103	34	31			
Clinical N stage[e]				0.008	<0.001	0.65
N0	273 (55)	100 (50)	143 (45)			

N1	162 (32)	88 (44)	151 (48)			
N2	9 (2)	11 (6)	15 (5)			
N3	1 (0)	0 (0)	0 (0)			
NX	54 (11)	6 (3)	7 (2)			
Surgical approach				0.13	0.014	0.039
Transthoracic esophagectomy	391 (90)	178 (92)	271 (94)			
Transhiatal esophagectomy	26 (6)	4 (2)	7 (2)			
Minimally invasive technique*	8 (2)	4 (2)	10 (3)			
Gastrectomy	9 (2)	7 (4)	1 (0)			
Missing data	65	12	27			

a) *Karnofsky performance score 0–100.* ***b)*** *American Society of Anesthesiologists physical status classification.* ***c)*** *Tumor location was assessed by endoscopy and computed tomography.* ***d)*** *Tumor stage (TNM) was assessed by endoscopy and computed tomography with optional use of endoscopic ultrasonography (EUS) and PET-CT.* ***e)*** *Clinical N stage was assessed by means of endoscopic ultrasound or FDG-PET-CT. *The code for minimally invasive esophagectomy was introduced in Sweden in 2014. Before that time, all procedures were classified as open surgery.*

Table 11. *Postoperative morbidity and mortality after esophagectomy due to cancer in the esophagus or gastro-esophageal junction, by preoperative treatment.*

	SA	**nCT**	**nCRT**	**SA/ nCT**	**SA/ nCRT**	**nCT/ nCRT**
	(%)				**p-value**	
30-day mortality	9 (2)	3 (1)	5 (2)	1.0	1.0	1.0
90-day mortality	22 (4)	10 (5)	23 (7)	0.79	0.081	0.27
Surgical complication[a]	100 (20)	61 (30)	82 (26)	0.005	0.048	0.34
Anastomotic leakage[b]	29 (6)	18 (9)	23 (7)	0.15	0.40	0.53
Bleeding[c]	7 (1)	6 (3)	5 (2)	0.22	1.0	0.36
Conduit necrosis[d]	10 (2)	6 (3)	9 (3)	0.42	0.48	1.0
Intra-abdominal abscess[e]	5 (1)	2 (1)	4 (1)	1.0	0.74	1.0
Intrathoracic abscess[e]	3 (1)	8 (4)	9 (3)	0.003	0.014	0.51
Severe lymph leakage[f]	7 (1)	10 (5)	12 (4)	0.006	0.027	0.55
Recurrent nerve paralysis[g]	16 (3)	5 (2)	14 (4)	0.81	0.45	0.34
Other serious surgical complication	37 (7)	18 (9)	30 (9)	0.54	0.29	0.78
Non-surgical complication[h]	119 (24)	57 (28)	75 (24)	0.27	0.97	0.30
Pneumonia[i]	36 (7)	21 (10)	23 (7)	0.18	0.97	0.23
Septicaemia[a]	19 (4)	5 (2)	20 (6)	0.36	0.010	0.042
Cardiovascular complication[k]	30 (6)	5 (2)	13 (4)	0.048	0.24	0.31
Pulmonary embolism[l]	7 (1)	6 (3)	8 (3)	0.17	0.24	0.79
Other non-surgical serious complication	54 (11)	28 (14)	33 (10)	0.29	0.87	0.27

Logistic regression of complications and postoperative mortality.						
	SA	nCT	SA	nCRT	nCT	nCRT
Non-surgical complications			**Odds ratio (95% CI):**			
Crude	1.0	1.23 (0.85-1.78)	1.0	0.99 (0.71-1.38)	1.0	0.81 (0.54-1.21)
Adjusted*	1.0	1.32 (0.82-2.12)	1.0	0.94 (0.59-1.48)	1.0	0.62 (0.38-1.01)
Surgical complications						
Crude	1.0	1.69 (1.17-2.45)	1.0	1.40 (1.00-1.95)	1.0	0.83 (0.56-1.22)
Adjusted*	1.0	2.01 (1.24-3.25)	1.0	1.32 (0.84-2.10)	1.0	0.77 (0.48-1.22)
Anastomotic leakage						
Crude	1.0	1.56 (0.85-2.88)	1.0	1.27 (0.72-2.24)	1.0	0.82 (0.43-1.55)
Adjusted*	1.0	1.81 (0.82-3.96)	1.0	1.22 (0.59-2.50)	1.0	1.01 (0.48-2.11)
90-day mortality						
Crude	1.0	1.11 (0.52-2.39)	1.0	1.70 (0.93-3.11)	1.0	1.53 (0.71-3.29)
Adjusted**	1.0	1.52 (0.58-4.01)	1.0	2.37 (1.06-5.29)	1.0	1.37 (0.57-3.29)

a) *Including anastomotic leakage, conduit necrosis, bleeding, abscess, chylothorax, recurrent laryngeal nerve paralysis, or other serious surgical complication.* ***b)*** *Anastomotic leakage was defined as a leakage diagnosed using CT scan with an oral water-soluble contrast medium, and any uncertainty was followed up with endoscopy.* ***c)****Bleeding more than 2 litres or need for surgical intervention.* ***d)*** *Clinically significant ischemia with perforation or ulcer.* ***e)*** *Radiologically or surgically verified abscess at least 3x3 cm.* ***f)****Lymph leakage requiring drainage for more than 7 days or surgical intervention.* ***g)*** *Diagnosed by an otolaryngologist.* ***h)*** *Non-surgical complications include cardiovascular complications, pneumonia, septicaemia, pulmonary embolism or other serious non-surgical complication.* ***i)*** *Pneumonia by chest x-ray findings, and fever, cough or dyspnoea.* ***j)*** *Body temperature above 101 F (38.3 C) or below 96.8 F (36 C), and a positive blood culture.* ***k)*** *Cardiovascular complications include cardiac arrhythmias requiring treatment, myocardial infarction, cerebral embolism, and pulmonary embolism.* ***l)*** *Radiologically confirmed emboli requiring treatment.*
**Adjusted for age, ASA score, histological tumor type, tumor location, and center.*
***Adjusted for age, ASA score, Karnofsky performance score, histological tumor type, and center.*

Table 12. *Pathological results and long-term survival of patients after esophagectomy due to cancer in the esophagus or gastro-esophageal junction, stratified by histological tumor type and preoperative treatment.*

	SA	nCT	nCRT	SA/ nCT	SA/ nCRT	nCT/ nCRT
Adenocarcinomas						
		n (%*)		**p-value**		
Number of resected lymph nodes, mean	23	22	15	0.24	<0.001	<0.001
Lymph node metastases	211 (72)	103 (61)	83 (45)	0.013	<0.001	0.003
R0 resection rate	246 (83)	145 (86)	175 (95)	0.49	<0.001	0.005
Tumor-free longitudinal margin	287 (97)	158 (93)	183 (99)	0.12	0.12	0.007
Tumor-free circumferential margin	252 (86)	153 (91)	176 (95)	0.13	0.001	0.09
Pathological T stage (median)	pT3	pT3	pT2	1.0	<0.001	<0.001
Histological complete response	-	8 (4)	40 (17)	-	-	<0.001
1-year survival	242 (77)	136 (83)	177 (82)	0.10	0.14	0.78
3-year survival	115 (45)	47 (49)	63 (43)	0.48	0.67	0.33
5-year survival	56 (31)	16 (35)	29 (33)	0.63	0.81	0.80
Squamous cell carcinomas						
Number of resected lymph nodes, mean	24	17	14	0.072	<0.001	0.22
Lymph node metastases	71 (62)	6 (33)	19 (30)	0.021	<0.001	0.77
R0 resection rate	95 (82)	15 (83)	63 (98)	0.88	0.001	0.009
Tumor-free longitudinal margin	107 (92)	18 (100)	64 (100)	0.22	0.022	1.0
Tumor-free circumferential margin	103 (89)	15 (83)	63 (98)	0.51	0.021	0.009
Pathological T stage (median)	pT3	pT2	pT2	0.009	<0.001	1.0
Histological complete response	-	4 (21)	19 (24)	-	-	0.78
1-year survival	94 (72)	16 (89)	60 (82)	0.13	0.11	0.49
3-year survival	38 (37)	8 (62)	25 (48)	0.082	0.17	0.39
5-year survival	24 (33)	3 (50)	14 (54)	0.41	0.066	0.87

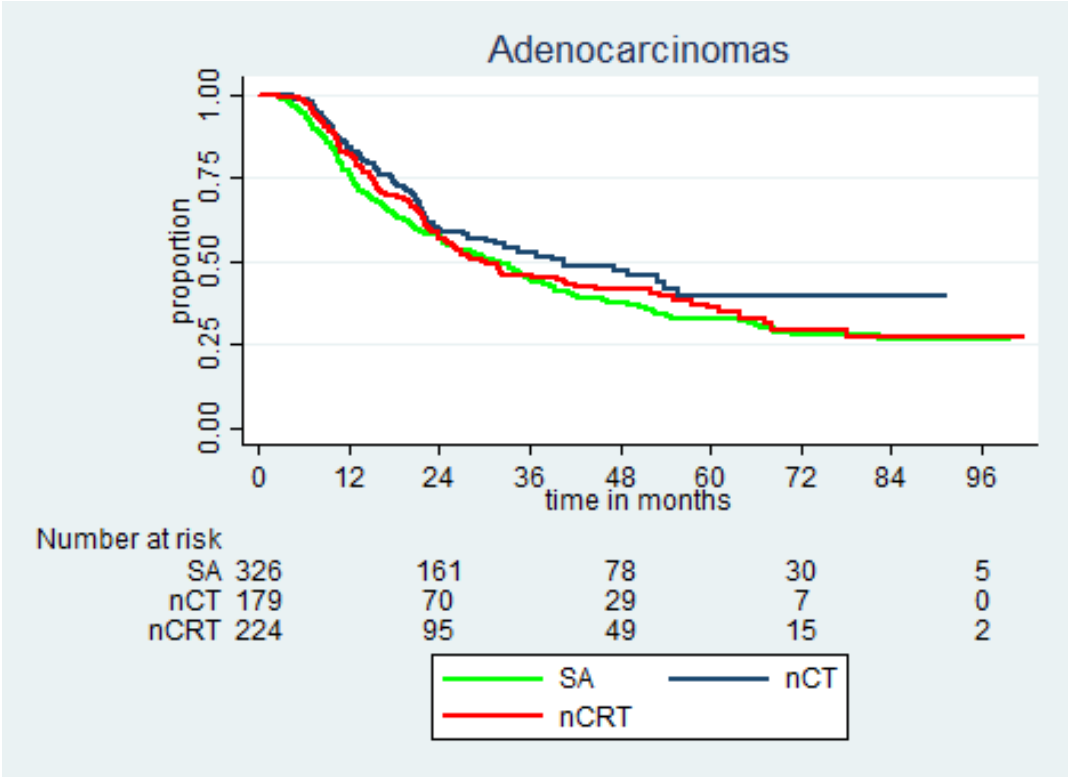
**=Percent of available patients for the stipulated analysis.*

Table 13. *Cox proportional hazard model of survival, by preoperative treatment, after esophagectomy in patients with cancer in the esophagus or gastro-esophageal junction, stratified by histological tumor type.*

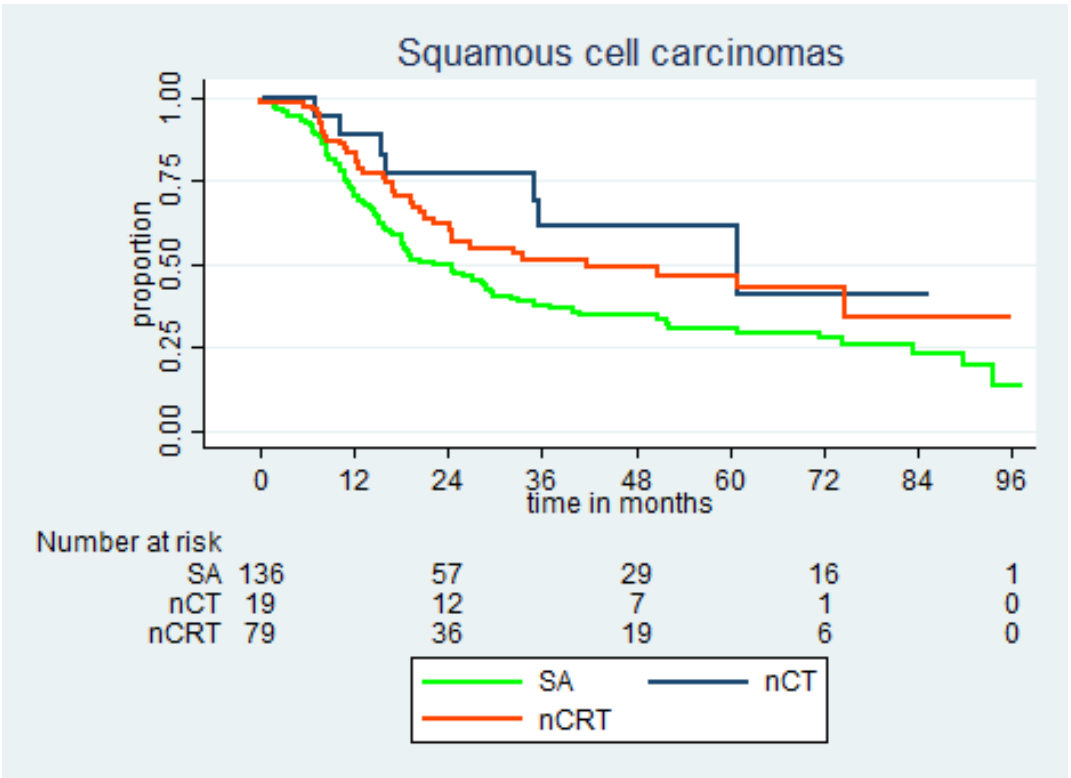
		SA vs. nCT		**SA vs. nCRT**		**nCT vs. nCRT**
			Hazard ratio (95% CI)			
Adenocarcinomas						
Crude	1.0	0.75 (0.57-0.97)	1.0	0.99 (0.71-1.38)	1.0	1.19 (0.89-1.58)
Adjusted*	1.0	0.93 (0.64-1.36)	1.0	1.07 (0.75-1.54)	1.0	1.13 (0.78-1.63)
Squamous cell carcinomas						
Crude	1.0	0.44 (0.20-0.95)	1.0	0.66 (0.45-0.97)	1.0	1.49 (0.66-3.34)
Adjusted**	1.0	0.39 (0.17-0.87)	1.0	0.74 (0.47-1.18)	1.0	1.55 (0.66-3.61)
Patients with ASA 1 and Karnofsky performance score 100						
Adenocarcinomas						
	SA	vs. nCT	SA vs. nCRT		nCT vs. nCRT	
Crude	1.0	0.70 (0.41-1.19)	1.0	1.00 (0.65-1.52)	1.0	1.43 (0.85-2.40)
Adjusted*	1.0	0.47 (0.21-1.04)	1.0	0.78 (0.39-1.55)	1.0	1.63 (0.81-3.28)
Squamous cell carcinomas						
Crude	1.0	0.46 (0.06-3.50)	1.0	0.54 (0.22-1.32)	1.0	1.21 (0.15-9.90)
Adjusted**	1.0	0.09 (0.01-1.09)	1.0	0.15 (0.04-0.59)	1.0	3.33 (0.33-33.47)

**Adjusted for age, sex, ASA score, cT stage, cN stage, year of treatment, and centre.*
***Adjusted for sex, ASA score, cN stage, year of treatment, and centre.*

***Figure 11**. Survival according to treatment group stratified by histological tumor type.*



Kaplan-Meier plot of overall survival, according to treatment, for patients who have undergone esophagectomy due to adenocarcinoma. SA vs. nCT: p=0.029, SA vs. nCRT: p=0.34, nCT vs. nCRT: p=0.24 (log rank test).



Kaplan-Meier plot of overall survival, according to treatment, for patients who have undergone esophagectomy due to squamous cell carcinoma. SA vs. nCT: p=0.032, SA vs. nCRT: p=0.032, nCT vs. nCRT: p=0.93 (log rank test).

5 DISCUSSION

5.1 METHODOLOGICAL DISCUSSION

5.1.1 Internal validity and precision

The quality of a study is determined by the internal validity and the precision. Internal validity depends on the level of systematic error, also called bias. The precision of a study reflects the degree to which repeated measures in unchanged conditions show the same results and indicates the impact of random error on the estimate. Random errors are impossible to exclude completely but if the sample size is adequate this problem will be controlled. The degree of random errors is statistically described in the p-values and confidence intervals of the estimates. Different study designs can increase the efficiency of the study and reduce the risk of bias. Systematic errors can be categorized in many different ways; I have used the three groups which are described below. When performing a study efforts are made to minimize each type of bias.

5.1.2 Selection bias

The idea of a clinical study is to investigate cause and effect of various factors. For example; patients with disease can be compared to healthy controls, or people who are exposed to a factor to people who are not exposed. In every study a selection of patients, a sample, from a source population needs to be made. This selection can potentially introduce bias. A selection bias occurs when the study population is selected based on factors associated with the exposure and outcome. The aim is to include a sample that is representative of the population in question. If patients are lost to follow-up in a study due to factors associated with the exposure and outcome this can introduce another type of selection bias. There are many different types of selection bias but all represent errors that occur as a result of the method of inclusion.

5.1.3 Information bias

In a scientific study large amounts of data are gathered. Some of the data will with most certainty be incorrect. This is also called misclassification. It can be caused by a human error, for instance typing 0 by mistake when the data point should be 1. This type of error is normally completely random and evenly distributed in the investigated groups. In this case it will typically not create a false association between exposure and outcome. This type of misclassification is called non-differential. If the non-differential error is large it will however hide or reduce and possibly conceal a true difference, so-called “bias towards the null”.

Another information bias is the differential misclassification which occurs when the errors are made with an association to the outcome and the exposure. This can create a false association or hide a truth. Recall bias is a potentially differentiated misclassification, for

example patients with disease can have a higher tendency to remember being exposed compared to healthy controls leading to a potentially overestimated risk of the exposure.

5.1.4 Confounding

Confounding is a systematic error that can be difficult to deal with. It can be explained as a mixture of effects. A classic example is that alcohol consumption is associated with lung cancer; however, this association is explained by the increased frequency of smokers among people who drink alcohol; i.e. the association is not true but a confounding effect of smoking. A confounder must be associated both to the exposure and the outcome, and it should not be an intermediate in the causal pathway from the exposure to the outcome. Randomization, restriction and matching are three ways to minimize confounding. When calculating the estimate it is also possible to adjust for confounders in a multivariate regression model. Residual confounding is the remaining error in an analysis after adjustments have been made. This can be caused by misclassification of confounding variables, unknown confounders, or adjustment in too wide categories. Confounding by indication can occur in observational studies because a group with an exposure can be different compared to the unexposed group because of the indication for the exposure. For example patients with more advanced tumors will receive more aggressive treatment with surgery and chemotherapy compared to patients with less advanced disease.

5.1.5 External validity

If a study has few systematic errors, and high precision, it has a potentially a high external validity. The study has measured the effect of the exposure in the sample in a correct way, reflecting the effect of the exposure in the source population. A study with high validity can be generalized to the population from which the sample has been selected, the so called source population. If the sample in that case is also representative of a larger population, for example the population of a country, the study results can be generalized, and expected to apply to, that population. If a study only includes women it can have high internal and external validity but the results may not be generalized to men because they were not included in the source population.

5.1.6 Case-control study

When investigating an uncommon outcome it is effective to use a case control study design. A number of subjects with an outcome are compared to a group of controls without the outcome. It is possible to examine the importance of many factors in the development of the outcome in a case-control study. To minimize confounding the controls can be matched on one or more variables, for example; age and gender. The selection of cases and controls, ant the matching, is a potential source of bias. A case-control study performed within a defined cohort it is called a “nested case-control study”. Case-control studies are relatively easy and cheap to perform, especially if the data is available.

5.1.7 Cohort study

When the exposure is rare it is more effective to start with an exposed group and compare it to a representative group of unexposed study subjects in a so-called cohort study. The design can be retrospective or prospective. Advantages of a cohort study are that more than one exposure and outcome can be examined, and that there is no risk of recall bias. Large prospective cohort studies can examine the effects of implemented treatment on a population and also investigate the causes of a disease over a long time period. Famous examples are the Framingham Heart study and the Nurse´s Health study.

5.1.8 Randomized controlled trial

A RCT is basically a form of cohort study where the exposure is randomly assigned to the study participants. RCTs are now the gold standard in clinical research for evaluating treatment effects. The advantage is that, as long as the sample size is fairly large, the randomization will create two groups that will be very similar concerning known and unknown confounding variables. The idea is that the only difference between the groups should be the exposure in question. The internal validity in a well-performed RCT is normally of high quality. The generalizability depends on the internal validity, the precision, and the selected study population. Disadvantages with the RCTs are that they are resource demanding, expensive and time consuming. It can also be difficult to study other associations than the ones predetermined. The study design requires a situation where it is unknown which of two treatments has better outcomes. For ethical reasons it is not possible to investigate the effect of possibly harmful exposures and risks of disease with an RCT.

5.1.9 Definitions of outcomes

It is important that the reported outcomes of a study are clearly defined. Concerning survival this can vary in several different ways. Survival analyses in a study can encompass different events depending on the definition. For example if you include; death by any cause, death attributable to the disease in question, or death attributable to other causes in the analysis the results will differ. Today there are no standardized definitions of these comparative terms in survival analyses (200). This needs to be clearly described for the reader to be able to interpret the results correctly. The definitions of end-points concerning postoperative morbidity and mortality are even more difficult to standardize. The postoperative period can be defined as the period until the patient is discharged, the so-called “in-hospital” period, or the first 30 days, or 90 days after surgery. If a patient is readmitted to the hospital due to a complication of the surgery it should be defined as a postoperative complication but this is not always the case. There is also a risk that the patient is admitted to another clinic and the information about the complication might not be known to the researcher performing the study, leading to misclassification of the variable.

Complications are defined and measured in many different ways. Information from a registry will in most cases include fewer events than a review of the patient´s chart performed by a dedicated investigator. The researcher can choose to include only serious complications or

count every small event that occurs in the postoperative period. Since there are no standardized definitions of postoperative complications it is important that the information about the applied definitions is stated in the report of the study. The Clavien-Dindo scoring system for severity of postoperative complications is a standardized system were the treatment or procedure following a complication is scored (66, 189-191). This system is validated in studies and enables researchers to compare the results of treatments in a more reliable way. It is also makes comparisons of different studies possible.

5.2 METHODOLOGICAL ASPECTS OF THE INCLUDED PAPERS

Papers I and III are based on the NeoRes trial which is a multicenter RCT. The evidence grade from an RCT is today regarded as the highest possible. Of course the trial needs to have high external validity for the results to be generalizable to larger populations. Every patient who was diagnosed during the study period was assessed for inclusion in the trial which decreases the risk for selection bias. The study was monitored by an independent research nurse to minimize missing data and misclassifications. The trial was unfortunately paused for a period of two years for administrative reasons, which delayed the completion of the trial. We evaluated the possible effect on the outcome that overall improvements, that have been made in the care of the patients from 2006-2013, could have introduced. A sensitivity analysis comparing the patients in the first years of the trial to the last period did however not show any differences compared to the combined results, which indicates that the time of treatment did not affect the outcome in the trial.

Paper II was a retrospective cohort study which in some aspects was challenging to analyse. The included groups were different at baseline concerning age, gender, ASA-score, and T-stage. The analysis of the study was difficult because of the risk of bias caused by these variances. We chose to handle this by limiting our analysis to the risk for, and severity of, anastomotic complications. The overall survival, and the overall CD score, were also interesting but due to the risk of bias and residual confounding these results were uncertain and therefore not analysed. A multivariate adjusted regression analysis was designed through step-wise univariate with testing of all potential confounding factors.

Paper IV has the strength of compiling a population-based cohort of more than 95% of all esophageal cancer patients in Sweden, thereby practically eliminating the risk of selection bias. A validation study has shown the data in the register to be highly accurate (196), indicating high external validity of the study. A down side of the registry-based study is that it is impossible to retrieve more information than that included in the registry. For example; detailed information about the neoadjuvant treatment concerning drugs and doses was unavailable. Further advantages with the design were the relatively large sample size, the complete follow-up concerning survival, and that practically all diagnosed patients, regardless of other characteristics, were included. This study effectively evaluates the effect of the implemented treatments on the Swedish population during these years.

5.3 GENERAL DISCUSSION

5.3.1 Paper I: Postoperative outcome after neoadjuvant treatment

In this work we were unable to detect any significant difference in the incidence of postoperative morbidity and mortality between the allocated treatments. However, complications were significantly more severe among patients who underwent resection after nCRT and there was a trend towards an increased incidence of respiratory and other nonsurgical complications in this group.

There are several possible mechanisms by which nCRT may affect the risk and severity of postoperative complications. As suggested in two retrospective studies, chemoradiotherapy may induce an acute impairment of cardiac function, with a dose-dependent decrease in ventricular ejection fraction after different combinations of chemotherapeutic agents and radiation doses. (201, 202) Moreover, chemoradiotherapy has been reported to be associated with an increased NT-proBNP release, which is a well-known marker for global heart failure and a strong predictor of postoperative cardiac events. (203, 204) In an analysis performed within the NeoRes-trial our group found that nCRT but not nCT had a negative impact on systolic and diastolic ventricular function (205). Platins and 5-fluorouracil, that were used in the present trial, especially 5-fluorouracil, may also cause specific cardiotoxic side effects, including myocardial infarction (206). It has been shown that increased fraction dose increases the risk for pericardial effusions after nCRT (207). In-depth knowledge of differences between nCT and nCRT regarding cardiotoxicity is, however, still largely lacking.

The effects of radiotherapy on lung tissue are well studied, and the risk of radiation pneumonitis is strongly associated with the mean total lung dose (208, 209). Radiation pneumonitis is an acute inflammatory response to lung irradiation and can lead to lung fibrosis. (210) The volume of lung tissue, that is exposed to doses of 5 Gy or higher, has been associated with an increased risk of postoperative pulmonary complications (211). Chemotherapy combined with radiation to the lung has been shown to decrease lung function when the local radiation dose exceeds 13 Gy and increases the risk of radiation pneumonitis, possibly influenced by a synergism between radiation and chemotherapy effects. (212, 213)

These and other factors may explain observations suggesting that patients' preoperative working capacity, as assessed during bicycle ergometry, is impaired by preoperative chemoradiotherapy. (214) On the other hand, a variety of factors, such as patient compliance, anemia, and cardiac and respiratory function, may also influence the results of the ergometry. Taken as a whole, this body of data emphasizes the importance of further studies elucidating the mechanisms through which cardiopulmonary toxicity may be induced by chemoradiotherapy.

The postoperative 90-day mortality rate among the patients resected after neoadjuvant treatment reflects the magnitude of the surgical trauma elicited by esophagectomy; the figures are comparable to the levels reported in previous studies (87, 117). The difference in 90-day mortality between the treatment groups is not statistically significant; however, the numeric difference is still noteworthy and also accords with previous findings (68, 117). The overall complication rate in the present study is likewise similar to that reported elsewhere (68, 117).

The two previous randomized trials of neoadjuvant chemoradiotherapy vs. chemotherapy; did not, using a limited sample size, detect any significant difference in postoperative morbidity or mortality. (117, 128) Despite this, the trial by Stahl et al. suggested an increased total postoperative mortality among irradiated patients similar to our experience (117).

Both the median Clavien-Dindo score and the mean comprehensive complication index score, were significantly higher after nCRT than after nCT, indicating that the complications after nCRT, albeit not with certainty more frequent, are in fact more severe.
There was a trend toward increased respiratory, cardiovascular, and total nonsurgical complications in the nCRT group. As the study was designed using complete histological response as the primary outcome variable, it is likely to be underpowered regarding the assessment of morbidity and mortality, making the absence of significant differences in postoperative morbidity and mortality between treatment arms possibly attributable to a type-2 statistical error.

In the most recently published randomized trial within the field, the CROSS trial, comparing nCRT with SA, the authors presented no indication of more complications or of increased mortality after esophagectomy and nCRT (87). The severity of complications was not reported in this trial. On the other hand, the recently published FFCD 9901 trial, which included only stage I–II esophageal cancer, but otherwise had a similar design to CROSS, showed a significant increase in postoperative mortality after chemoradiotherapy (118) compared to SA. Interestingly, this trial reported no difference in the overall frequency of postoperative complications, which was also the case in our trial. In the CROSS trial, the balance between adenocarcinomas and squamous cell cancers was 75% to 25%, whereas the relation was the opposite in FFCD 9901. Regarding surgical technique, this was not specifically reported in the CROSS trial, but the transhiatal approach was probably common, whereas the patients in FFCD 9901 underwent a transthoracic esophagectomy. In the present trial most patients underwent a transthoracic esophagectomy, and few were operated on using a transhiatal approach, which precluded a meaningful subgroup analysis regarding importance of the surgical approach. It is possible that nCRT may have a more severe effect on postoperative complications after transthoracic resection than those submitted to a transhiatal resection. Regarding the role of the histological subtype and the associated comorbidity profile, postoperative mortality may increase after neoadjuvant treatment predominantly in patients with squamous cell cancers, but not so in patients with adenocarcinomas, as suggested by our recently published meta-analysis (68). Owing to its

limited number of patients with squamous cell cancers, the present study could not address this hypothesis.

5.3.2 Paper II: neoadjuvant chemoradiotherapy and cervical anastomosis

In paper II we found that the vast majority of patients receiving nCRT before esophagectomy with cervical anastomosis were due to be irradiated at the site of the anastomosis in the gastric conduit. There was no difference in the incidence of anastomotic complications between the nCRT group and the non-RT group. However, when anastomotic complications occurred in the nCRT group, they were much more severe, with a manifold increased risk of organ failure requiring ICU care.

The finding that preoperative radiation within a standard nCRT protocol included a significant radiation dose to the future gastric conduit and the site of the gastro-esophageal anastomosis raises serious concern and calls for improvement in the coordination of radiotherapy dose targeting and surgical approach. Another potential reason for inadvertent radiation of the future site of anastomosis is that patients generally are not required to be fasting, either before the dose planning imaging or during the radiotherapy treatment sessions. This may, depending on the degree of filling of the stomach, at each treatment session, cause variations in how much of the stomach wall is included in the radiation field.

Our finding that nCRT is associated with significantly more severe cervical anastomotic complications, although the incidence is not increased, is consistent with other studies showing increased postoperative risk for patients undergoing nCRT compared to SA or to neoadjuvant chemotherapy alone followed by surgery (118, 215). There are also studies that do not show increased risk for postoperative morbidity and mortality after nCRT, but these studies do not present the severity of the complications (86, 87, 216, 217). None of the earlier studies focused on cervical anastomoses alone, and none of them showed such a large increase in the severity of complications after radiation as we observed in the present study.

These findings raise the question of possible mechanisms for neoadjuvant nCRT to increase the severity of cervical anastomotic complications without clearly increasing the incidence. Evidence is accumulating to show that the addition of radiation therapy, in the given dose ranges, elicits discrete but defined impairments in both systolic and diastolic left ventricular function (205). Moreover the physical endurance of these patients may be compromised as well (214, 218), the consequences of which may well affect the resilience to otherwise manageable complications. Another, more speculative potential explanation could be that irradiation to the gastric fundus may cause anastomotic leaks by a partly different mechanism, compared to leaks unexposed to irradiation, perhaps with more influence of conduit necrosis.

This study has several limitations. The small sample size limits the precision and prevents subanalyses. Moreover this is a retrospective observational study and accordingly there is a substantial risk of bias. On the other hand, the patients included comprised all esophagectomies performed due to cancer and reconstructed with a cervical anastomosis

during the time period. The nCRT group and the non-RT group were not comparable as regards factors such as age and comorbidity. In fact, the non-irradiated patients were both older and had more comorbidity. These differences would normally act in such a way as to conceal a detrimental effect of radiation, but despite this, the nCRT patients in the unadjusted analyses had a threefold increased risk of organ failure due to anastomotic complications, compared to non-exposed patients. This difference was shown to even further increase after adjusting for the confounding factors as mentioned above.

This study suggests that radiation, administered within a standard 40 Gy nCRT protocol, exposes the future anastomotic site of the gastric fundus to doses that may well impair healing of the subsequent cervical anastomosis Our data further suggest that nCRT may increase the clinical severity of anastomotic complications. Moreover, this study raises two important questions: 1. Do the findings regarding a substantial radiation targeting of the gastric fundus reflect broader clinical practice? 2. Does nCRT with partial radiation exposure of the future gastric conduit really cause cervical anastomotic complications of a more severe magnitude? These issues deserve serious scientific attention in large prospective studies.

5.3.3 Paper III: neoadjuvant chemotherapy vs. chemoradiotherapy

In this RCT, which compared nCT with nCRT treatments for esophageal and GEJ carcinoma, we have shown that nCRT significantly increases the proportion of complete histological response, increases the occurrence of N0 lymph-node status, and increases the R0 resection rate, but does so without a corresponding improvement in survival. Moreover, we have shown that patients who respond to the neoadjuvant treatment with tumor regression have significantly increased survival compared to patients without, or with a poor, response.

Cisplatin and 5-fluorouracil still remain among the most well documented chemotherapeutic regimen choices in neoadjuvant chemotherapy and chemoradiotherapy for esophageal cancer (102, 128, 219, 220), although in recent years other alternatives have gained increasing popularity. In our present trial many patients had difficulty tolerating the full three cycles of chemotherapy in the nCRT arm and consequently only 74% completed three cycles, compared to 85% in the nCT arm. The number of cycles of platin-based chemotherapy needed for optimal anti-tumor effect has recently been studied in the British OE05 trial. In this trial Alderson et al showed that 4 cycles of epirubicin/cisplatin/capecitabine increased the tumor regression grade and that there were trends towards improved disease-free and progression-free survival for patients with gastro-esophageal adenocarcinomas compared to 2 cycles of cisplatin and 5-FU. The toxicity was however increased and overall survival did not improve (156).

This trial compared three cycles of neoadjuvant platin-5FU-based chemotherapy with a combined chemoradiotherapy regimen using the same chemotherapy but adding 40 Gy of radiotherapy. With some variations, both of these neoadjuvant therapy options have in recent decades been frequently used in clinical practice and in several trials (102, 171, 221) and both may be regarded as belonging to the standard neoadjuvant treatment options at the time this

trial started. These regimens have over the years undergone revisions, and in addition to the regimens used in this trial, the currently practiced adjunct therapy options in many Western countries are (i) neoadjuvant chemotherapy with two cycles of cisplatin and 5-fluorouracil in accordance with the OE02 trial (104, 220), (ii) perioperative chemotherapy modified after the MAGIC protocol (103), and (iii) chemoradiotherapy utilizing the CROSS trial regimen with chemotherapy, combining weekly paclitaxel and carboplatin with concomitant radiotherapy, totalling 41.4 Gy (87). Regarding the perioperative MAGIC type chemotherapy using epirubicin, oxaliplatin, and capecitabine/5-FU; although it may seem quite different from the nCT used in the present trial, it is clear that this therapy, especially for esophageal cancer patients, mainly rests on the neoadjuvant component because postoperative therapy can be administered to only about half of the patients. In the CROSS trial-chemoradiotherapy regimen, the radiotherapy is similar, while the chemotherapy is likely to have a lower systemic anti-tumor effect than the chemotherapy used in the present trial.

The analysis in paper I showed that complications in this trial were significantly more severe after the addition of radiotherapy, and this is further supported by the analysis of the causes of death by follow-up year, which showed significantly more deaths unrelated to disease progression in the nCRT arm during the first year of follow-up. Several studies have shown that nCRT carries an increased risk of postoperative death compared to SA, a trend that has not been observed at all after nCT (68, 116, 118). Given the clearly superior complete histological response rate after nCRT compared to nCT, we surmise that the reason there is a lack of a corresponding advantage in overall survival may be that the combined impact of chemotherapy and radiotherapy takes a heavy toll by significantly increasing deaths by serious adverse events and complications during the first year of follow-up.

Interestingly, the analysis of survival by histological tumor type revealed a trend towards improved survival after the addition of radiotherapy among patients with SCC and, conversely, a trend towards poorer survival with the addition of radiotherapy among patients with AC. The latter trend towards a survival disadvantage after the addition of radiotherapy in AC patients has to our knowledge not been described previously and, of course, given the lack of statistical significance, can be discussed only in a hypothesis-generating context. One reason for this difference in trends could be that the two previous studies comparing nCT and nCRT did not publish any per protocol survival data. Another reason may be that both these trials used a lower radiotherapy dosage, 30 and 35 Gy, respectively (117, 128). The toll of increased short-term non-cancer-related deaths in the nCRT arm affects patients with both histological tumor types; hence, the opposite survival trends for the two subtypes are puzzling but may be explained by the higher radiation sensitivity in SCC, leading to an overall beneficial effect of combination therapy in this histological type.

Among the strengths of the study, it should be mentioned that the NeoRes trial is the largest randomized trial to date comparing neoadjuvant nCT and nCRT for resectable esophageal and GEJ cancer. The randomization was computerized and performed by an independent institution, stratifying for histological type. The two study groups were well balanced in the

distribution of age, gender, comorbidity, and tumor characteristics. Both the neoadjuvant therapy and surgical procedures were rigorously standardized in accordance with the protocol. No patients were lost to follow-up. A single expert pathologist, blinded to treatment allocation and outcomes, reviewed all surgical specimens. A limitation of the study is that it was designed to distinguish a difference in complete histological response and is hence underpowered for the survival analyses. The many early deaths not related to cancer progression in the nCRT arm illustrate the need for less toxic preoperative regimens with preserved efficacy.

5.3.4 Paper IV: Population based data

In paper IV we show that elderly patients, with more comorbidity but less advanced tumors, were more often treated with SA, than with bi- or trimodal therapy. The proportion of patients given neoadjuvant treatment continuously increased during the study period. Both types of neoadjuvant treatment seem to increase the risk for postoperative morbidity. Additionally both neoadjuvant regimens increase the overall survival in patients with squamous cell carcinomas, while patients with adenocarcinomas had no statistically significant benefit in overall survival after neoadjuvant treatment, although subgroup analysis including only fit patients without comorbidity showed a strong trend towards increased survival after treatment with nCT compared to SA. A small group of patients with SCC received nCT (n=19) with good results, but the limited sample size makes interpretations uncertain.

The neoadjuvant chemotherapy regimens used in Sweden during the study period either comprised three preoperative cycles of platins and 5-FU or perioperative administration of three + three cycles of platins, 5-FU and epirubicin, according to the MAGIC protocol (103). These regimens use a higher total dose of chemotherapeutic agents compared to what has been used in most randomized clinical trials (103-105, 152, 161). These differences may well explain the increased frequency of surgical complications recorded after nCT in this study, contrary to what has previously been seen (68). We also found that nCRT increased the risk for postoperative mortality, which has previously been shown in some trials (68, 116, 118). The observational design of the study makes treatment selection with regard to disease severity a potential source of bias. Tumor stage and comorbidities have been included in the applied multivariate regression model in order to adjust for these differences. The missing data was slightly higher in the SA group concerning some baseline characteristics, which has been considered in the analysis through complete case analysis.

In the setting of clinical trials patients are carefully selected for inclusion, while in this population-based study, all patients operated on with curative intention have been analysed. These patients are, as a group, likely to have more comorbidity and lower performance status than those selected for a trial. This may possibly explain the gap seen between the significant survival benefit in adenocarcinoma from both types of neoadjuvant therapy over SA in randomized trials compared to the findings in this observational study. A subgroup analysis of high performance status patients without comorbidities indicates an enhanced effect on survival of neoadjuvant treatment in this group; this, in a way, mimics the selection practiced

in clinical trials, thus suggesting that outcome after neoadjuvant therapy might improve if patients were selected accordingly in clinical practice as well.

Previous RCTs have used radiotherapy in a dose ranging from 18.5-45 Gy, most often 40 Gy, in combination with chemotherapy (86, 87, 116, 118, 158, 170-172). The RCTs that have compared nCRT to nCT showed increased tumor regression and R0 resection rates, but there is no detectable gain in survival compared to nCT (117, 128). The results from RCTs of neoadjuvant treatment and SA have displayed slightly improved survival and no increased risk for complications, which need re-evaluation in large prospective studies (68, 102). The results of our present study are consistent with previous trials with increased tumor regression, R0 resection rates, pathological node negative disease, and risk of treatment related mortality after nCRT, although with no difference in overall survival. The SA group displays a survival that is comparable to that after neoadjuvant treatments for adenocarcinomas in this cohort. The available evidence for an advantage from nCT and nCRT for patients with high age and severe comorbidity is weak. This could, perhaps together with some residual confounding from lower T- and N- stages, explain the relatively good results seen after SA in this study. Patients with adenocarcinoma treated with SA have a survival after multivariable adjustment for confounders similar to that of the patients that received neoadjuvant treatment and a likely benefit was only seen with nCT in patients with high performance status and without comorbidity. Regarding patients with squamous cell carcinoma this study confirms previous findings from Asia regarding a survival benefit with nCT (93) and Western evidence (87) regarding nCRT, albeit in this study again only statistically significant regarding high performance-low comorbidity patients. Further studies are needed to find a regimen with decreased risk of adverse events, and to define which groups benefit from nCRT. The ongoing trials Neo-AEGIS and Topgear, are comparing nCT and nCRT for esophageal and gastric cancer, and the results of these well-powered trials have the potential of changing standard practice (222, 223). Based on this study's results, one can argue that nCT should be the treatment of choice for esophageal and GEJ adenocarcinomas.

In this study fewer lymph nodes were examined by the pathologists after nCRT compared to nCT and SA, which is in line with previous studies showing that neoadjuvant chemo-radiotherapy decreases the number of detected lymph nodes, malignant as well as benign (86, 87, 117). A recent study has shown that the number of examined lymph nodes after nCRT was not a predictor of survival (224). nCRT increases the R0 resection rate and decreases lymph node metastases compared to SA and nCT without increasing survival for patients with adenocarcinomas. The reasons that this favourable tumor response did not translate into improved survival are still unclear and need to be addressed in future studies.

The major strengths of this study are the nationwide, population-based design, covering more than 95% of all esophageal cancers diagnosed in Sweden, the complete follow-up, the prospectively collected data, and the large sample size. A limitation of this study is that it was not possible to validate postoperative complication data. Unfortunately, detailed information about the neoadjuvant treatments could not be found in the registry. Regarding postoperative

morbidities, completing the Clavien-Dindo score for severity of postoperative complications was not possible due to the fact that this classification was not introduced until quite recently. Patients were not randomized to the different treatment groups, which results in potential confounding; this was, however, dealt with in the multivariable analyses. There is always a risk for misclassification of both the exposures and the outcomes, but it is reasonable to assume that these are evenly distributed in the treatment groups (196). There were some missing data (cT stage, cN stage and tumor location), but in the multivariate adjusted models, complete case analysis was performed and no missing data affected the survival analyses.

In conclusion, this large, nationwide prospectively-collected cohort study, which addressed the impact of neoadjuvant therapy as clinically practiced in an unselected, defined population, shows a survival benefit after both types of neoadjuvant treatment for patients with esophageal squamous cell carcinoma. An overall survival benefit was not seen for patients with adenocarcinomas. Neoadjuvant treatment was associated with an increased risk of postoperative morbidity and, after nCRT, even postoperative mortality.

6 CONCLUSIONS

nCRT is not associated with a higher overall incidence of postoperative complications after esophagectomy than nCT.

nCRT may increase the clinical severity of cervical anastomotic complications.

The complications that occurred in patients who received nCRT were more severe than after nCT.

There was statistically significant higher mortality, unrelated to cancer progression, in the nCRT group during the first year after diagnosis compared to nCT.

Radiation, administered within a standard 40 Gy nCRT protocol, exposes the future anastomotic site of the gastric fundus to doses that may well impair healing of the subsequent cervical anastomosis.

The addition of radiotherapy to neoadjuvant chemotherapy increases the complete histological response and R0 resection rates and decreases the proportion of patients with lymph node metastases.

This thesis does not provide any evidence in support of using complete histological response as a surrogate marker for survival in the comparison of neoadjuvant therapies.

Both nCT and nCRT improves survival for patients with esophageal squamous cell carcinomas compared to SA.

An overall survival benefit of neoadjuvant treatment was not seen for patients with esophageal adenocarcinomas.

Neoadjuvant treatment was associated with an increased risk of postoperative morbidity and, after nCRT, even postoperative mortality in an unselected population based cohort.

In summary, this thesis shows that the use of nCRT as a standard treatment for esophageal and junctional adenocarcinomas may be questioned and that nCT could be a better alternative.

Patients with esophageal SCC probably have an increased postoperative risk after nCRT compared to nCT but the gain in survival makes the treatment reasonable. Patient selection is likely very important in order to reach a positive outcome.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Cancer i matstrupen (esofagus) är en tumörsjukdom som är förknippad med dålig prognos. Sjukdomen drabbar främst medelålders män men i vissa fall även yngre personer. Ungefär 20% är kvinnor. Riskfaktorer för esofaguscancer är rökning, alkoholöverkonsumtion, övervikt och stora problem med halsbränna. Den klassiska behandlingen av esofaguscancer är att operera bort tumören inklusive matstrupen och ersätta den genom att skapa en tub av magsäcken som förs upp i bröstkorgen. Detta är en mycket stor och krävande operation som leder till komplikationer i 30-50% av fallen, och ger ungefär 25-30% chans till 5-årsöverlevnad. På senare år har forskning visat att det är fördelaktigt att ge behandling med cellgifter eller kombination av cellgifter och strålbehandling innan operationen utförs. På så sätt har chansen till långtidsöverlevnad ökat något. Avsikten är att tumören ska krympa inför operation varvid chansen ökar att den går att operera bort i sin helhet. Behandlingen minskar också risken för spridning av tumören till lymfkörtlar. Risken med att ge förbehandling är att komplikationer efter operation kan öka och att patienten kan bli så påverkad av behandlingen att operationen inte kan utföras. Det är visat att de patienter som svarar på behandlingen genom att tumören krymper har klart bättre prognos än de som inte svarar. I vissa länder används cellgifter som förbehandling och i andra kombinerade behandlingar med strålning. Innan vår studie gjordes fanns bara två randomiserade studier som jämfört cellgifter med kombinations-behandling.

Vår grupp har under 2006-2013 randomiserat 181 patienter i Sverige och Norge med operabel esofaguscancer till förbehandling med cellgifter eller kombinationsbehandling. Arbete I är en analys av de första 90 dagarna efter operationen. Resultaten visar att båda grupperna får komplikationer lika ofta, men att utgången var klart sämre i gruppen som fått strålning inför operation. Arbete III är en analys av hur många patienter som svarat på behandlingen med krympning av tumören och av 3-årsöverlevnad. Resultaten visar att kombinationsbehandling ger klart ökad krympning av tumören men vi såg inte att det ledde till någon överlevnadsvinst. Arbete II är en analys av 70 patienter som opererats på Karolinska Universitetssjukhuset för esofaguscancer med sammankoppling av magsäck och matstrupe gjord ovanför bröstkorgen via halsen. Resultaten visar att den delen av magsäcken som används i kopplingen ofta får ganska höga stråldoser innan operationen, vilket kan påverka läkningen. Vi såg också att de patienter som behandlats med kombinationsbehandling inför operation hade större risk att utveckla allvarliga komplikationer jämfört med övriga. Arbete IV är en sammanställning av alla patienter som registrerats i Sveriges Nationella Register för Esofagus- och Ventrikelcancer, vilket är mer än 95% av alla cancerfall under denna period. Totalt inkluderades 1020 patienter som delades in i grupper beroende på behandling. Resultaten visade att förbehandling med cellgifter eller kombinationsbehandling ger ökad chans för krympning av tumören men ingen överlevnadsvinst för patienter med tumörtypen körtelcancer. De som hade skivepitelcancer och förbehandling hade ökad överlevnad. Båda typerna av förbehandling ökade dock risken för komplikationer och dödsfall i samband med operation.

Sammanfattningsvis visar denna avhandling att förbehandling med cellgifter och strålning ger ökad tumörkrympning och överlevnad för patienter med skivepitelcancer men troligen till priset av ökade risker i samband med operation. För patienter med körtelcancer sågs inte någon överlevnadsvinst av tilläggsbehandling med strålning.

8 FUTURE PERSPECTIVES

We will continue to study neoadjuvant treatment for esophageal and junctional carcinomas. Patient selection is an interesting issue to investigate further. The factors that determine a patient's response to neoadjuvant treatment will be studied. Patients with histological complete response can be compared with non-responders possibly in a case control study. Another interesting issue is the use of biochemical markers to identify patients that will respond to the neoadjuvant treatments. Methods for determining complete response without esophagectomy, and possibly avoid surgery in these patients, will be developed.

With the introduction of minimally invasive surgical techniques, and improved postoperative recovery with modern approaches and enhanced recovery programs, the use of adjuvant treatment could change in the future. The planning of the neoadjuvant radiation field in relation to the site of the anastomosis on the gastric fundus is an important issue.

Concerning histological tumor type it is now clear that esophageal AC and SCC are to be considered as two different cancers and studied separately in future trials. Definitive chemoradiotherapy for patients with SCC is a very interesting option for the future. Optimization of the nCRT and nCT strategies will continue and hopefully new drugs can be developed to increase the chances for survival in esophageal cancer.

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